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Part one

Journal of Global Health: The Mission Statement

The *Journal of Global Health* is a peer-reviewed journal published by the Edinburgh University Global Health Society, a not-for-profit organization registered in the UK. The *Journal* publishes editorials, news, viewpoints, original research and review articles in two issues per year.

The *Journal*'s mission is to serve the community of researchers, funding agencies, international organizations, policy-makers and other stakeholders in the field of international health by:

- presenting important news from all world regions, key organizations and resources for global health and development;
- providing an independent assessment of the key issues that dominated the previous semester in the field of global health and development;
- publishing high-quality peer-reviewed original research and providing objective reviews of global health and development issues;
- allowing independent authors and stakeholders to voice their personal opinions on issues in global health.

Each issue is dedicated to a specific theme, which is introduced in the editorial and in one or more viewpoints and related articles. The news section brings up to five news items, selected by the *Journal*'s editorial team, relevant to seven regions of the world, seven international agencies and seven key resources important to human population health and development.

We particularly welcome submissions addressing persisting inequities in human health and development globally and within regions. We encourage content that could assist international organizations to align their investments in health research and development with objective measurements or estimates the disease burden or health problems that they aim to address. Finally, we promote submissions that highlight or analyse particularly successful or harmful practices in management of the key resources important for human population health and development.

All editors and editorial board members of the *Journal* are independent health professionals based at academic institutions or international public organisations and so are well placed to provide objective professional evaluation of key topics and ongoing activities and programs. We aim to stay true to principles of not-for-profit work, open knowledge and free publishing, and independence of academic thought from commercial or political constraints and influences. Join us in this publishing effort to provide evidence base for global health!

March 7, 2011   The Editors, *Journal of Global Health*

Children suffering from diarrhoea in intensive care unit at the hospital in Dhaka adjunct to International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B). At the beginning of the 21ˢᵗ century diarrhoea was a major cause of child mortality, causing nearly 2 million child deaths each year world-wide. Since then, a broad distribution of oral rehydration sachets (ORS), much improved school enrolment for girls, and widespread maternal education on symptom recognition and intervention reduced this burden to under 500 000 deaths per year. Still, more should be done and it is expected that a roll-out of rotavirus vaccine may further reduce this unacceptable death toll.

Measuring coverage of essential maternal and newborn care interventions: An unfinished agenda

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Over the past few decades, the agenda for newborn health has shifted remarkably, taking newborns from being nearly invisible in the global health agenda of 1990s to being central in discussions today. Despite this change, the decline in neonatal mortality from 1990 to 2016 has been slower than that of post–neonatal under–five mortality: 49% compared with 62% globally [1]. Newborn deaths represent 46% of all under–five deaths–of the 5.6 million under–5 deaths in 2016, nearly 2.7 million deaths occurred in the neonatal period, with a large proportion dying within the first week following birth [1,2]. Preterm birth complications (35%), intrapartum–related events (24%) and sepsis (15%) – most of which are preventable–have been identified as leading causes of neonatal deaths [3]. Although maternal mortality was estimated by the UN inter–agency group to have declined by 44% between 1990 and 2015, the reduction was far below the 75% MDG target. Approximately 303 000 women die each year from complications of pregnancy and childbirth, with 99% of deaths in low– and middle–income countries, making maternal mortality one of the indicators with the largest disparity between rich and poor countries [4]. With the majority of maternal and newborn deaths occurring around the time of birth, quality and equitable maternal and newborn care are essential to improve survival. Several global partnerships and initiatives such as the United Nations Every Woman Every Child movement (EWEC) and Every Newborn Action Plan (ENAP) have called for more focused attention on newborn health in order to end preventable newborn and child deaths [5,6]. The 2030 agenda of Sustainable Development Goals (SDG) and accompanying Global Strategy for Women's Children's and Adolescents' Health (2016–2030) include a specific target for all countries to reduce neonatal mortality to at least as low as 12 per 1000 live births, further reinforcing and strengthening commitment to neonatal survival [7].

Available research and evidence on newborn health clearly highlight impending challenges and strategies to improve newborn survival. The 2013 PLOS Medicine collection on "Measuring Coverage of MNCH" and the 2014 Lancet Every Newborn Series noted gaps in the availability of metrics and data on newborn care. Additionally, the globally agreed upon monitoring frameworks as ENAP, Ending Preventable Maternal Mortality (EPMM), the Global Strategy for Women's, Children's and Health (2016–2030) and Countdown to 2030 – have all identified critical areas where further indicator development and data collection are needed and have begun work to test or validate indicators [8]. There is also increased recognition of the role of data in measuring progress toward the promise of an equitable future in the SDG era. This has

resulted in an explicit SDG target to support countries to increase the availability of high–quality, timely and disaggregated data, including data related to newborn health.

To date, large–scale household surveys such as the UNICEF–supported Multiple Indicator Cluster Surveys (MICS) and the USAID–supported Demographic and Health Surveys (DHS) are the primary sources of population–level coverage estimates of newborn health interventions [9,10]. Household surveys have been extremely important for national and sub–national monitoring of key indicators and are invaluable as a public source of data for examining sub–national inequalities and understanding coverage gaps in intervention as well as for research purposes. However, studies have indicated that the validity of coverage measures from household surveys can vary across indicators [11–13]. Household survey programs work constantly on revisiting and refining approaches to data collection. Following the 2013 recommendation of the Newborn Indicators Technical Working Group, some new indicators to measure care in the immediate newborn period have been added by the two household survey programmes. In addition, newborn–care related content is now also included and measured through health facility assessments.

With the increasing focus on the need for data on newborns, and availability of new data, it is time to understand these data and take stock of the findings but also of gaps. In the current context in which newborn survival is central to the global health agenda, there is an urgent need to strengthen the collection of data on newborn care, particularly on aspects related to quality of care and to identify and fill remaining gaps as well as ensure the data are aligned with global and national monitoring needs. Attuned to this context, the series of papers in this collection provide program and policy findings on measurement of maternal and newborn care and outcomes, with implications for future measurement implementation and research. The supplement provides an analysis and description of the associations and patterns of coverage and quality of recommended maternal and newborn care practices and interventions as captured at the population and facility level. It further strengthens evidence of limitation of current coverage indicators and the need for effective coverage measurement that incorporates quality of care provided. Several papers in the supplement highlight the scope of facility level data in assessing readiness to provide newborn care. Finally, the supplement assesses gaps and quality of available data on newborn health and measurement approaches across measurement platforms.

MEASURING PROGRESS AND CHALLENGES IN NEWBORN HEALTH

Newborn health–related measurement (data and metrics)

Improving measurement of newborn health is at the core of this supplement. Though the quality, frequency and visibility of data for newborn health have improved notably compared to a decade ago [14], gaps in availability and quality of data on newborns remain. To accelerate and monitor progress towards the global target of reducing neonatal mortality, a set of core indicators has been proposed and incorporated in several monitoring frameworks. Some core indicators like, skilled birth attendant and exclusive and early initiation of breastfeeding have been established and reported on for decades through data collected in MICS, DHS and other household surveys. As a result, nearly 75% of the countries have data available for these indicators [8,15]. On the other hand, some indicators used for global reporting, such as "postnatal care for mothers and newborns," have been agreed upon more recently, with essential care indicators such as "thermal care" recommended for data collection in household surveys only in 2013. As highlighted by Sitrin et al in this supplement, only twelve national surveys between 2005 and 2014 included at least one indicator for immediate newborn care in addition to breastfeeding [16]. The supplement includes a series of papers addressing gaps and assessing the quality of many of these core indicators. Main findings are described below (**Table 1**).

Postnatal care (PNC) is an important strategy to improve newborn survival. Some issues related to measurement of postnatal contacts were mentioned in the PLOS One series, "Measuring Coverage of MNCH"; it also described a few changes made to MICS and DHS questionnaires, in an attempt to address issues revealed through formative research on indicator for postnatal care. However, there has not been a systematic assessment comparing the measurement approaches implemented by MICS and DHS, the two largest sources of population–based MNCH coverage data in low and middle–income countries, which left open the question of how questionnaire differences may affect the comparability and interpretation of PNC coverage across surveys and countries. The study comparing measurement of postnatal care across the two survey programs in this supplement reveals a difference in the way questions on postnatal care

Table 1. Data on newborn indicators across current global monitoring frameworks and assessed in the current collection

Newborn health–related indicators	Gaps (as identified in the current series)	Recommendation (based on studies in the series)
Content of antenatal care	Large gap between contacts and content of antenatal care	Coverage indicators should include some elements of content of care to identify true effectiveness of maternal and child health interventions.
Skilled attendant at birth	Skilled attendants even in health facilities may not be equipped to save newborns	Need to supplement and link coverage data with health facility level data and quality of care indicators.
Postnatal care for mothers and babies	Difference in data collection tools eg, questionnaires and the methodology adopted to measure PNC across survey programs has created comparability issues in coverage levels	Need to harmonize data collection tools across survey programs. Need to determine differences in coverage by individual, household, regional characteristics. Individual characteristics should include delivery–related factors.
Essential newborn care with early initiation of breastfeeding as tracer indicator: • immediate and thorough drying; • immediate skin–to–skin contact; • delayed cord clamping; • early initiation of BF	• Early initiation of breastfeeding is not a high performing tracer indicator of essential newborn care, • Coverage of skin to skin and thermal care is low	Need to collect data on newborn care practices other than breastfeeding initiation through standardized questions in household level surveys.
Service readiness for newborn care in facilities	Lack of qualified staff	Improve training and increase capacity of staff across health sectors. Increase availability of essential commodities

for mothers and newborns are framed in MICS and DHS. MICS and DHS surveys have also followed different methodological approaches to compute the global indicator of postnatal contacts for mothers and newborns within two days following delivery, resulting in comparability issues in coverage levels across the two programs. As the evidence shows, this has implications for accurate measurement of coverage of postnatal care [17]. With an increased focus on quality of care provided, content of postnatal care may provide more helpful monitoring information to track reduction of neonatal mortality in the future.

The Every Newborn Action Plan proposed several indicators to track impact, coverage and equity of newborn health–related interventions. It proposed early breastfeeding as a tracer for essential newborn care, due to the data availability and evidence of benefits of breastfeeding. A methodological paper in this series assessed the correlation between early breastfeeding initiation and other newborn care practices [16]. The analysis found that breastfeeding initiation is not a good tracer indicator for newborn care practices and recommends improved methodologies for accurate measurement of these practices.

The quality of newborn health interventions is a significant gap that is not currently being addressed by the globally agreed upon coverage indicators to assess newborn health. It is increasingly recognized that global measures of coverage of maternal and newborn health capture main contacts with the health system but provide little information about the quality of care received. In this supplement, we assessed the gap between contact and content –as a proxy for quality–of maternal and newborn health services in 20 sub–Saharan countries and found that the gap between contact and content is excessively large in all [18].

Newborn health policy and program

Over the past several years, there have been major advances in agenda setting for newborn health, including implementation of several globally endorsed action plans and monitoring frameworks. There has been a notable increase in the number of publications focused on newborn health, and evidence is now available for interventions that address the three main causes of newborn deaths. Recent research indicates that increased coverage and quality of preconception, antenatal, intrapartum, and postnatal interventions by 2025 has the potential to avert 71% of neonatal deaths (1.9 million, range 1.6–2.1 million) [19]. A study in this supplement analyzed the recently available data on newborn care practices and found very low coverage of skin -to -skin contact despite its protective effects against neonatal morbidity and mortality [20]. Singh et al. examined the role of individual and health system characteristics on receipt of postnatal care and found coverage to be low in Bangladesh, particularly for newborns of mothers who delivered at home and who did not report a complication. Such analysis result in better identification of the most vulnerable newborns and provide valuable programmatic insights to improve coverage [21].

Quality of newborn health interventions emerged as a key missed opportunity to accelerate newborn survival in three studies that analyze survey data from 20 sub–Saharan countries, Bangladesh and Haiti [22–

24]. Two studies using health facility data assessed the service readiness to deliver life-saving newborn interventions and found that health facilities are not yet equipped to save newborns at risk of dying [23,24]. An assessment of health service environment in Malawi revealed that newborns in districts with high service readiness have higher odds of receiving essential newborn care. This study highlights that there is an urgent need to increase the level of service readiness across all facilities and in particular, the quality and training of the staff, so that all newborns – irrespective of the health facility, district or region of delivery–are able to receive all recommended essential interventions.

RECOMMENDATIONS – CALL TO ACTION

Poor quality in newborn care is a major barrier to newborn survival, and we strongly recommend strengthening measurement of elements of content of care to improve the measurement of the coverage of maternal, neonatal and child health care. Recently, the World Health Organization and the Lancet quality improvement commission have proposed standards of care and measures assessing quality of maternal and newborn health care [25,26]. We propose that linking household survey data on coverage of interventions with facility–level data on service availability and readiness could help better measure effective coverage and identify its determinants and barriers.

It is encouraging to note that newborn health measurement is now central to many global initiatives, and new indicators are being added to household surveys and facility assessments. However, to track progress over time and make comparisons between countries, there is an urgent need to harmonize data collection across household surveys and facility assessments. To assess whether newborns are receiving life–saving interventions, the existing standardized questions regarding newborn care practices such as thermal care and skin–to–skin contact need to be consistently added to national household surveys. The DHS now includes an optional newborn module which outlines standardized questions on newborn care, which could be added to DHS surveys. MICS also includes standard questions. However, there is some evidence of poor validity of household survey indicators especially related to timing or sequence of events around the time of birth or questions which are composite of several events such as breastfeeding within one hour of birth, newborn dried and placed on mother's skin. For instance, these studies confirm that many indicators of intrapartum care and associated morbidities have generally low validity and reliability when assessed by women's reports. However, some salient indicators are reported with acceptable accuracy, most notably skilled attendance at birth and cesarean section. [12,27]. Other strategies must be developed for those indicators with low validity and reliability and caution must be taken when interpreting results. Newborns also require data that can inform the decisions of more local health system actors. At the district level a manager who wants to optimize the health system can use national survey data to benchmark indicators at the regional level once every three to five years. But to know which inputs and health worker processes are optimized in the district, where actions are needed, and crucially whether outcomes improve as a result, different data platforms are required. The Health Management Information System (HMIS) and a well-functioning civil registration and vital statistics system have the potential to support this need and innovations to summarize and visualize these data so fit for district-level management could play an important role. Currently, UNICEF, WHO, and UNFPA are developing a standardized list of indicators for maternal and newborn health that can be consistently tracked and reported through HMIS and DHIS2. Other projects, such as the Maternal and Child Survival Program and the Quality, Equity and Dignity Network are testing and implementing these indicators, with a focus on using data for decision making at all levels. Data from HMIS will be crucial for monitoring progress toward national and global targets.

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Development of global health research in China

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With the continuous deepening and broadening of China's engagement in global health as well as the transformation of its role in global health governance, global health science have made great strides in China, from the infancy stage of last century to the grown-up stage of this century. Considerable progress in global health discipline has been witnessed, especially in the last ten years. The rapid development of global health in China is characterized with three crucial indications: the rise of global health institutions, the ever-expanding research team and the growing number of global health researchers, and also the increasing number of relevant papers published in international journals.

Ten years ago, there was not any domestic institution specializing in global health research, let alone a nationwide research network in global health. In 2007, Peking University took the lead in establishing the Global Health Research Center, which became China's earliest research institute in this field. Subsequently, other universities, such as Fudan University, Wuhan University, Duke Kunshan University, Zhejiang University, Central South University, Sun Yat-sen University and so on, set up global health centers or research institutes. In 2011, the undergraduate major in global health was set up in Wuhan University. In 2012, the first global health department nationwide came into being under the School of Public Health, Peking University. In addition to those universities, China National Health Development Research Center and Chinese Center for Disease Control and Prevention (China CDC), as the official policy research institute and national public health agency under the leadership of National Health and Family Planning Commission of China (NHFPC), have also set up divisions that engage in global health research or practice. On this basis, ten universities jointly initiated the Chinese Consortium of Universities for Global Health (CCUGH) in 2013. It is the first cross-school organization in global health research field in China. Soon afterwards, in 2015, the China Global Health Network was established, involving not only universities but also government agencies, China CDC, pharmaceutical companies and other research and development (R&D) organizations. In 2016, the Global Health Branch was set up under Chinese Preventive Medicine Association. With the support of NHFPC, the Ministry of Commerce, and some international organizations such as China Medical Board (CMB) and UK Department for International Development (DFID), Chinese academia sets off an upsurge of research into global health, systematically studying how China's experience and lessons learnt in health development can be shared with other developing countries, exploring global health governance and health development assistance. Additionally, Fudan University and China CDC have also started pilot projects on maternal and child health and malaria control in Myanmar and Ethiopia. Based on all those researches, more and more articles on global health are being published.

The development of global health research in China should be attributed to three major contributing factors.

First, under the context of China's overall development and diplomatic development, its practice in global health over the years play a key role. As early as 1963, China started to dispatch overseas medical teams to Algeria. Chinese medical teams are now working in 49 countries. The health cooperation between China and other countries has also extended to the public health field since 2013. For example, health professionals were dispatched to combat Ebola and Middle East respiratory syndrome (MERS) coronavi-

rus and went to Madagascar to fight against plague. China also cooperated with the US CDC to help African countries set up their own CDCs. All of those practical efforts lay a good foundation for Chinese academia to carry out global health researches.

Second, investments made by the Chinese government in scientific research and the scientific research ability of Chinese researchers are improving. In 2016, a total of about yuan 1.57 trillion was invested in R&D, an increase of yuan 150.69 billion or 10.6% over the previous year [1]. In 2013, the expenditure on health research and development in China reached 46.84 billion yuan, accounting for 4.11% of the total nationwide R&D expenditure [2]. The increasing research expenditure has created a material foundation for Chinese researchers.

Third, extensive international cooperation in line with the reform and opening-up policy is a prerequisite for the development of global health research in China. With the deepening of reform and opening-up, the exchanges between China and the world are getting more and more frequent. As General Secretary Xi Jinping noted in the report to the 19th CPC National Congress, the major-country diplomacy with distinctive Chinese features should promote the building of a new type of international relation and the fostering of a community of shared future for mankind [3]. An increasing number of Chinese scholars are joining in international cooperation. These exchange and cooperation processes also provide opportunities for global health researchers.

Despite progress made so far, China is still facing challenges in global health research. It is manifested from several aspects. Global health is still a relatively new concept in China. As an interdisciplinary field, it requires attention from various disciplines. However, current researchers in this field are mainly public health professionals and the capacity of personnel engaged in global health research needs to be enhanced. Moreover, it is necessary for more people to go board and identify needs for this field so that China can cooperate with more international counterparts and provide public health products worldwide. Therefore, there is still some way to go for China in global health. Nevertheless, as China marches on in reform and opening-up and actively takes more and more international responsibilities, it is believed that more people will join in the global health field, facilitate global health research and present more research achievements to the international community.

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▶ Africa

▶▶ The number of new malaria cases in Gambia fell by 40% between 2011 and 2016, whilst the prevalence of the parasite in children aged under 5 years fell to 0.2% from 4% over the same period. Gambia could be the first country in sub–Saharan Africa to eliminate malaria, but faces a shortfall in funds for the most difficult "last mile" in reaching the goal of no new malaria cases by 2020. It has a funding gap of US$ 25 million, and the possibility of "donor fatigue", whereby donors turn their attention elsewhere as cases drop, but the country's new leadership, under the democratically elected President Adama Barrow, may reinvigorate the fight against malaria. In addition to the usual control measures such as antimalarial drugs, bednets and spraying, Gambia has deployed technology to tackle malaria, using GPS, mobile devices and online platforms to track the implementation of the standard control measures, aided by improved internet bandwidth in rural areas. (*Reuters*, 12 July 2017)

▶▶ The 2017 South Africa Health Review paints a bleak picture of South Africa's health sector, as it battles to deliver services and reduce costs in the face of stagnant economic growth. Health expenditure will increase by 1.1% in 2016/17, 0.8% in 2017/18, and will be cut by R142 million (US$ 10 million) in 2018/19 – a 0.1% reduction. The rand has fallen 38% against the US$ from 2012 to 2016, which had hugely increased cost pressures, whilst an additional 400 000 people each year are joining the HIV treatment programme, and many new children's vaccines have been introduced. However, the costs of ARV drugs have been kept down thanks to the central procurement of medicines. Staff costs are the main expense – and most provinces have imposed restrictions on filling vacant posts, and 300 medical specialists left between 2015 and 2016. Spending on infrastructure has also been cut, and more patients are being referred to clinics rather than hospitals, to save money. However, clinic visits have been cut by 3 million in the past 2 years – although a new medicine dispensing programme enables some patients to collect their medication from designated pick–up points such as private pharmacies and schools. And finally, the management skills essential to contain costs is in short supply in the health sector. (*Daily Maverick*, 23 August 2017)

▶▶ Nurses in Kenya ended a five–month strike, which had crippled the country's health system, especially maternity, surgical and inpatient services. Kenya's Council of Governors agreed to pay nurses an initial uniform allowance of Sh15 000 (US$ 145) – an increase from its current Sh10 000 (US$96) level. Nurses will also receive a risk allowance of between Sh20 000 and Sh25 000 (US$193 – 242) each year, depending on their role. All disciplinary cases against striking nurses will be withdrawn, and salaries will be reinstated before 31 December, and Kenya's regions are beginning to recruit nurses after a jobs freeze. "Over 85% of Kenyans living below the poverty line cannot afford expensive healthcare, and therefore we call off the strike" said Mr Seth Panyako, the KNUN secretary–general. (*The Nation*, 2 November 2017)

▶▶ There have been 91 deaths from snake–bites within 3 weeks in Nigeria, but the Federal Government moved to refute rumours that public hospitals have ran out of antidotes to snake bites. Prof Isaac Adewole, Nigeria's Minister of Health, confirmed that the Ministry of Health still has some vials of anti–snake venom in stock, from its 2016 procurement exercise where states and other treatment centres were supplied upon request. He noted that the states (Gombe and Plateau) where the 91 deaths occurred had not compiled with the new system of procurement–upon–request; and that 5 states so far have requested anti–venom stocks. He called upon states to invest in their own procurement of anti–venom treatments, and warned that the Federal Government cannot continue to procure and distribute the venom without charge. "The Federal Government is however working on Public Private Partnership arrangements for local production of anti–snake bite venom which will make the product available, affordable and accessible," he said. (*allafrica.com*, 8 November 2017)

▶▶ Zimbabwe has made progress in reducing HIV prevalence from 27% in the 1990s to less than 15% in 2017, but those of its HIV–positive citizens living in extreme poverty face daily battles against the corruption and prejudice which limits their access to vital treatment, support and care. Mr Robert Mugabe's resignation offers Zimbabwe a chance to revitalise its HIV strategy to ensure that no–one is left behind – by prioritising and fast–tracking actions for the poorest and most marginalised people. Zimbabwe's Health Ministry must continue to strengthen HIV programmes that target women and girls, disabled people, the elderly, prisoners and people in remote rural areas, sex workers, people in same–

sex relationships and those in extreme poverty. All these groups suffer discrimination and disadvantage, and have higher risks of preventable and premature death from HIV. The government has a moral responsibility to prioritise these groups so that development does not benefit wealthier groups initially, and therefore widening inequalities. Investing in the already–piloted Electronic Health Records, which can provide high–quality data security, storage and analysis, will be essential for a low–income country with high HIV prevalence to deal with high treatment needs. Corruption must also be tackled – Zimbabwe is one of the most corrupt nations on earth – and poorer people, especially marginalised groups living with HIV/AIDS rely on public services weakened by the misappropriation of funds. (*The Conversation*, 30 November 2017)

Asia

▶▶ Mr Taro Aso, Japan's finance minister and a lifelong smoker, recently expressed doubts about the link between smoking and lung cancer. His ministry also benefits (by US$ 18 billion a year) from tax revenues on tobacco products, and owns about 33% of Japan Tobacco, the world's fourth–largest cigarette–maker. Controversy has intensified recently as the government proposes a ban on smoking inside public buildings to protect citizens against passive smoking, which kills 15 000 people in Japan each year. A group of MPs from the country's Liberal Democratic Party are campaigning against the proposed ban, supported by tobacco farmers and the restaurant industry, who fear that banning smoking from their premises – which accounts for most passive–smoking deaths in Japan – would lead to mass business closures. Japan's health ministry believes that these fears may be overstated, as non–smokers appreciate clean air (following successful health campaigns, 18% of Japan's adults smoke). Another contradictory aspect of Japan's smoking legislation is that some cities ban public smoking on streets, whilst only encouraging smoking to be banned indoors. This often leads to smokers moving indoors to smoke, rather than smoking outside. (*The Economist*, 22 June 2017)

▶▶ To date, Sri Lanka's Ministry of Health recorded at least 300 deaths and more than 100 000 infections caused by a major dengue outbreak. Heavy monsoon rains, rain–soaked garbage, standing pools of water and poor sanitation all provide ideal living conditions for the mosquitoes which transmit the virus. The International Federation of Red Cross and Red Crescent Societies (IFRC) is expanding its emergency assistance to Sri Lanka with the Sri Lanka Red Cross in order to suppress the spread of the disease. IFRC stated that the hospitals are stretched to the limit, especially in the Western Province. According to the WHO, dengue, endemic in 100 countries with an estimated 390 million cases of infection annually, is ranked as one of the world's fastest growing diseases. Dengue is recognisable by its flu–like symptoms that can lead to the deadly hemorrhagic dengue fever. There appears to be no end in sight for dengue danger as "the virus currently spreading has evolved and people lack the immunity to fight off the new strain," says Novil Wijesekara, of the Sri Lanka Red Cross. (*Reuters*, 24 July 2017)

▶▶ A group of anonymous civil society organisations, people living with HIV, and others, have written to the Global Fund to express "grave concern" over its funding to combat HIV in Cambodia, as well as the allocation process. The Global Fund is the main donor in the country's efforts against HIV/AIDS, TB and malaria. The group expressed concern that civil society representatives have had little input into decision–making, and that participation in Cambodia's Community Co–ordinating Mechanism (CCM) – a national multi–sectoral committee in charge of facilitating Global Fund activities in the country – is skewed towards international representatives. As a result, the civil society organisations wish to step down from the CCM. These organisations are also concerned that funding is being targeted towards international NGOs, rather than local organisations working with key affected populations. In response, the Global Fund confirmed that it is planning a consultation with these groups to discuss their concerns in a transparent manner. It also noted that out the Global Fund's US$ 41.6 million allocation to Cambodia for 2018–20, 27% is set aside for NGO–led activities. (*Phnom Penh Post*, 30 October 2017)

▶▶ Winter storms are building over northern Afghanistan, bringing snow to the mountains, thunderstorms to Kabul, rain to Lahore and Islamabad in Pakistan – and helping to clear the smog hanging over the region. Pakistan has experienced traffic accidents – with 10 people killed and 25 injured in 2 weeks – linked to poor visibility, and it also causes respiratory problems. Mr Mohammad Riaz, a Pakistani meteorologist,

said that the smog is caused by dust, pollution, the burning of crops, factory and brick kiln emissions, and is expected to linger until mid–November. He advised people to wear face masks to protect themselves from respiratory ailments. Average air pollution in Pakistan's main cities is 4 times higher than World Health Organization limits, and although overall air quality in 2017 is better than 2016, pollution levels in Lahore recently reached 18 times the healthy limit. Inevitably, as the winter weather settles, an increase in pollutants will again thicken smog to "very unhealthy" or "hazardous" levels – with human activity being the main contributor. (*Al Jazeera*, 16 November 2017)

▶▶ North Korea has banned most forms of birth control, and as a result condoms are increasingly in demand as a gift item brought back by business travellers returning from China, according to sources in North Korea. Condoms are prohibited for manufacture or sale in the country, and are blocked from entry at customs posts, and they are officially considered "indecent items". North Korea's leader, Kim Jong Un has strongly encouraged a high birth–rate. However, the high costs of education and raising a child means that most couples limit themselves to one child, although medical professionals are banned from offering birth control and abortions, in order to raise the country's falling birth rate. Moreover, despite being banned, sex work is widespread in North Korea, making the easy availability of condoms even more essential. (*Radio Free Asia*, 20 November 2017)

▶ Australia and Western Pacific

▶▶ Throughout the developing world, cervical cancer is the main cancer affecting women – in 2017, an estimated 266 000 women world–wide will die from it, and 85% of them will be in developing countries. Rates of cervical cancer in the Pacific Islands are also concerning, with Melanesia being particularly at risk, with an incidence rate of 33.3/100 000 women and a mortality rate of 20.7/100 000 women. Cervical cancer can be prevented, but a systematic review of cervical cancer in the region found that its preventative programmes are inadequate despite the region's high incidence rates. It would cost an estimated US$ 2.1 million to vaccinate all 13–year old girls against HPV, which is highly affordable, particularly if obtained through a regional bulk purchase underpinned by collective bargaining. The region has an opportunity to prioritise cervical cancer through the Framework for Pacific Regionalism, which could boost the number of countries offering HPV vacation from 60 to 80%. Improved and integrated sexual and reproductive health services would also boost cervical cancer survival rates, but political will and increased resources are essential. (*Radio New Zealand*, 21 July 2017)

▶▶ According to UNAIDS, Papua New Guinea saw a 4% increase in new HIV infections between 2014 and 2016, with an estimated 2800 new infections in 2016. This follows on from a 41% decline in HIV infections from 2001 to 2009. With prevention efforts stalling, Papua New Guinea needs to reinvigorate its response but it faces a number of obstacles in ending the HIV epidemic as a public health threat by 2030. These obstacles including criminalising sex work and consensual same–sex sexual activity, high rates of gender–based violence, and the challenges of extending health services to the country's rapidly–growing young population. (*Radio NZ*, 25 July 2017)

▶▶ Australia's federal government spends US$ 4.6 billion each year on private health insurance subsidies, and the consumer group CHOICE has called on it to stop providing tax breaks and rebates for "junk" health insurance policies. These policies do not cover treatments for most illnesses, including heart attacks, stroke and cancer, or only allow the policy–holder to be treated as a private patient in a public hospital. According to CHOICE, junk policies account for 13% of all hospital and combined policies on the insurance market, but cover less than 1% of hospital treatments and services. Generally, they cover a very small number of procedures, including accidents, wisdom teeth and appendix surgery, but exclude all others. Consumes are attracted to them because of the tax breaks on offer, or without realising that they bought a dud policy with little value, and many end up with "bill shock" when they discover that their treatment is not covered by the policy. "These policies are not only poor value for consumers, but are poor value for the Australian community, who subsidise junk policies than do not reduce the strain on the public healthcare system," CHOICE argues. They also called for simplified health insurance policies, after its survey found that 44% of policyholders found it difficult to compare policies. (*Sydney Morning Herald*, 4 August 2017)

▶▶ Nationally, an unusually higher number of mumps cases was reported across New Zealand, and the country's Ministry of Health warned of "an increased risk of further outbreaks." The University of Otago is offering its students free measles, mumps and rubella booster shots to students who are unsure of their vaccination history, or who have not had two MMR vaccinations since 1990, following an outbreak of 10 cases. Auckland reported 51 cases in the past month – mainly amongst young people, and several were recorded in Waikato and two in Nelson. Auckland's Regional Public Health Service has expressed concern over immunisation levels. Although most people recover from mumps, it can have serious complications, including inflammation of the tissue surrounding the brain (meningitis), inflamed testicles or ovaries, and deafness. (*stuff.co.nz*, 17 August 2017)

▶▶ According to the 2016 Global Burden of Disease, 1–in–5 Australians has a mental illness or a substance abuse disorder – and despite having one of the highest life expectancies in the world, and being a world leader in treating heart disease, stroke and cancer, on the whole Australia is failing to improve its mental health. The burden of mental illness has improved little over the past 20–30 years, and the findings of the Global Burden of Disease study comes one day after the Royal Australian College of General Practitioners announced that mental health is the main condition dealt with by general practitioners. Moreover, although life expectancy is increasing in Australia, the average man will live the 10 years of his life in ill–health, and the average woman will live the last 12 years in ill–health. Mental illnesses, eg, depression, anxiety, bipolar, posttraumatic stress disorder and substance abuse account for nearly 25% of the years spent in ill–health by Australians. According to Laureate Professor Alan Lopez of Melbourne University and one of the study's co–authors, this is partly due to the difficulties in treating mental illness. "There's no easy fix for mental health issues. Their epidemiology, the age at which they begin and just the fundamental nature of mental illness means that it is an intensive care, long treatment process. It doesn't mean that we don't have treatments, it just means that they take longer. And people don't always go for treatment as well – often they just live with their disability," he says. (*Huffington Post Australia*, 17 September 2017)

▶ China

▶▶ At the Chinese Communist Party's 18th Congress in 2012, China's government pledged to eliminate rural poverty by 2020, and to pull at least 10 million people from rural poverty each year, from 2016 onwards. Based on China's official poverty line of 2300 renminbi (US$ 333) per year, the number of rural poor fell from 555 million in 1995 to 56 million in 2015. However, despite the falling number, China still faces a smaller, yet tougher, poverty problem. China's social assistance programme, *dibao,* is a minimum living standard programme that targets poor households below a certain income, but despite being a national programme, it is implemented locally. A World Bank report from 2015 found that 90% of rural individuals with annual income below the threshold level did not receive *diabo* from 2007–09, echoing a report from Beijing Normal University which found that over 80% of eligible households did not receive *diabo* from 2010–11. However, poverty alleviation measures such as *diabo* are ultimately only emergency mechanisms. To truly tackle China's poverty, the government must combine reforming *diabo* with more tailored poverty relief measures on a case–by–case basis. There is evidence that this is under way in some places, with local governments targeting poor individuals with health problems; but in the long–term, the idea that jump–starting economic growth in less–developed areas is sufficient to end poverty must be abandoned. (*East Asia Forum*, 26 May 2017)

▶▶ According to the 2017 Future Health Index from Philips, China has the lowest concentration of skilled health professionals (31.5 per 10 000 people) out of the 19 countries surveyed, combined with a high risk of crippling health care costs for surgical procedures. This situation has further deteriorated over the years, worsened by the country's focus on disease–curing rather than prevention, hospital overcrowding and lack of access. The country's government is aiming to improve access and affordability for its 1.3 billion citizens, moving from disease–centred care to "big health", to deliver a full range of health services covering the entire care continuum, with an emphasis on health management and chronic disease management. One of the main areas of reform is the decentralisation of China's multi–tiered health care system to streamline resources and improve effectiveness, and – crucially – all hospitals will share resources, expertise and information to ensure cost savings. China is also embracing big data to enable precise di-

agnosis and personalised health care – currently, too few data are collected or organised in a way that can be analysed. The government is focusing on accelerating the roll–out of the disease–based standard clinical data repository across a range of areas, and by 2020 three digital national databases will be established, incorporating health information, health profiles and medical records. (*China Daily*, 27 June 2017)

▶▶ In an interview with *The Diplomat*, Peter Fuhrman of China First Capital Ltd, talked about the looming health challenge of Alzheimer Disease in China. He recognises that the treatment of chronic diseases, with Alzheimer at the forefront, is the largest single challenge to the country's health system. China has made massive progress in the transformation from a rudimentary health system to expanding health coverage to all areas of the country and the vast majority of its citizens. However, this has in part led to increasing life expectancy, which has reached Western levels, and now China faces the strain of millions of older people suffering from conditions without any real treatment options. Mr Furhman calls for China to foster the development of quality treatment centres for Alzheimer patients, to lengthen and enrich their lives. This will require investments in buildings as well as specialist staff. Finally, he highlights how China is set to have 50% of the total number of people with Alzheimer Disease by 2045, and has less than 500 specialist treatment beds – overall, chronic care offers excellent investment opportunities for overseas companies. (*The Diplomat*, 26 September 2017)

▶▶ China and Canada are collaborating on a US$ 1.69 million project to improve mental health treatment through the use of smartphone apps, text messaging and electronic medical records. The project, EMBED, aims to close the mental health care gap, as both countries struggle with shortages of mental health care professionals – especially in remote areas, and overburdened staff. There is potential for the app to target younger people who feel comfortable on digital platforms, and it could eg, raise an alert if a student withdraws from a class or social activities. Other apps could help someone through a crisis or depressive episode, when the individual may not wish direct contact with a mental health professional. There is much debate on the impact and potential dangers than smartphones may have on mental health, but with positive use they could help those with mental health needs. "Achieving economic health takes a comprehensive approach, and it is innovation like the Digital Hub [the project host] that will help develop new approaches to improving mental wellness on an unprecedented global scale," said Canada's International Trade Minister, François–Philippe Champagne. (*CBC.ca*, 9 November 2017)

▶▶ Rising incomes and an underfunded – albeit universal – health system are driving urban residents towards private health care insurance. According to a recent survey by Financial Times Confidential Research, 21.7% of people have some private medical cover in addition to the state programmes. Coverage is highest amongst high–income householders – 42.5% – and amongst residents of first–tier cities, where 25.8% of residents have private insurance, compared to 17.4% in third–tier cities. Insurers across China have reported brisk sales of health policies in 2017, despite restrictions on the sales of investment–linked policies. Compared to the USA, where just 16.2% of people buy their health care insurance directly, 43.5% of people in China who buy insurance buy it directly. Indeed, China's employers already contribute a percentage of employee salaries to the state programme and are therefore normally reluctant to pick up the costs of additional cover. However, more companies are expected to offer private health care to win or retain talent, although it is expected that self–financed premiums will remain the biggest driver of growth in this market. (*Nikkei Asian Review*, 14 November 2017)

▶ Europe

▶▶ More than 7200 people in Romania have contracted measles since late 2016, and 30 people – mostly children – have died. This outbreak has affected several countries in Europe, with the largest outbreaks in Romania and Italy, but France, Germany, Poland, Switzerland and Ukraine are also affected. The World Health Organization (WHO) recommends two doses of vaccinations, covering 95% of the population, to ensure immunity and prevent outbreaks. However, in Romania only 80% of children receive the first dose, and 50% the second dose, due to poverty, a shortage of vaccines and poor access to health care. In response, the Romanian government is pushing through legislation that would make vaccination obligatory for children to attend school. The problem is compounded by a growing number of parents who refuse to have their children vaccinated, and some religious groups and public figures launching anti–vaccination campaigns. (*Medical Xpress*, 23 June 2017)

NEWS

▶▶ Singapore faces growing number of professionals using drugs, and with 66% of new substances users under the age of 30 years, its Home Affairs and Law Minister has warned of a new generation of drug users. Singapore is looking to other countries, including Iceland and Finland, for models on tackling the problem. Iceland has experienced falling numbers of young people using alcohol, cigarettes and cannabis, eg, in 1998 42% of people aged 15 or 16 years of age said that they had been recently drunk – compared to 5% in 2016, and the country now has the lowest substance use by teenagers in Europe. Iceland's success is evidence–based, and includes connecting with young people, health education, involving parents in their children's lives and focusing on preventive factors that decrease young people's changes of substance misuse, plus reducing risk factors that lead them to it. Eg, parents are urged to spend more time with their children, and to ensure that they are home early. Finland has local drug prevention and outreach efforts, and all areas offer free activities, such as sports, for young people. Other young people are encouraging to act as "peer educators" to their fellows on the dangers of drugs, and like Iceland, Finland has also seen declining drug use amongst its young people. (*Strait Times*, 27 June 2017)

▶▶ Russia faces severe problems with the distribution of HIV/AIDS medication, leading to many patients to rely on each other to access treatment, in an echo of the film, *The Dallas Buyers' Club,* which was set in 1980s USA. Clinics frequently run out of medication supplies in the middle of the year, leaving patients with life–threatening gaps in their treatment – so patients began to organise and distribute drugs themselves. Eg, patients whose treatment regime had changed would send their old medication for redistribution, or – tragically – through patients who had died. Drug companies have informally provided medication, via sympathetic workers and personal contacts. Russia is almost unique amongst developed countries in having increasing numbers of new HIV infections and AIDS–related deaths. Campaigners estimate that deaths will top 20 000 in 2017, up from 18 577 in 2016, although it is impossible to say how many deaths result from erratic medication supplies. Alesei Yaskovich, part of the Aptechka network for redistributing HIV medication, hopes to create a single online resource where all pharmacy managers could post real–time information about their drugs supplies. Russia's shortages of HIV medication is partly a result of Western sanctions, but the country's pharmaceutical companies are not filling the gap. (*Radio Free Europe*, 8 October 2017)

▶▶ According to Anna Sarzynska, owner of the Anna Dental Clinic in Gdansk, Poland, around 80% of her patients come from aboard, particularly Scandinavia but also the UK and Ireland. This is part of a trend of rising medical tourism in central and eastern Europe, which has been growing by 12%–15% each year – and in 2016, 488 000 people came to Poland for treatment. To date, the region has specialised in simple treatments that do not require prior consultation, and patients are attracted by prices that may be 2–3 times lower than at home. The growth in medical tourism is bolstered by a 2013 EU directive, which enables patients to obtain treatment in any member state and have it refunded if it is covered by their own national health care schemes. The region is also attracting patients from former Soviet republics, who often lack easy access to medical services and equipment. Mr Artur Gosk, head of the Polish Association of Medical Tourism, calls for more government support for medical tourism, and others point to Turkey – a popular destination for less complicated procedures, enhanced by government efforts, such as discounts for patients flying with Turkish Airlines and plans to introduce tax–free health care zones. However, the growth in medical tourism is not necessarily leading to improvements in public services, especially in hospitals – illustrated by Poland spending 6.4% of its GDP on health care – one of the lowest levels in the EU. (*Financial Times*, 20 October 2017)

▶▶ Research from MacMillan Cancer Support and Public Health England shows that 17 000 people have survived for several years after diagnosis with 10 types of stage 4 cancer. The results of this research was revealed at the 2017 National Cancer Research Institute Conference in Liverpool. It is based upon data from England's public health registry, capturing data on people who were diagnosed with one of 10 common types of cancer between 2012 and 2013, and were still alive at the end of 2015. MacMillan Cancer Support said that these figures demonstrated the changing nature of cancer, and that patients whose prospects were previously limited could see their cancers become more "treatable" and manageable, like other chronic diseases. Other studies have suggested that cancer survival rates in the UK lag behind other European countries, and experts call for earlier diagnosis and improved access to treatments. Dr Jem Rashbass, cancer lead at Public Health England, described the registry data as "an invaluable resource in helping us to track improvements in cancer outcomes and gain more understanding of the implications for those living with and beyond a cancer diagnosis." (*The Guardian*, 8 November 2017)

▶ India

▶▶ India comprises 20% of the world's population, yet the DNA sequences of its people makes up just 0.2% of global genetic databases – indeed, 81% of global genetic information is collected from people with European ancestry. According to Sumit Jamuar, the chief executive of Global Gene Corp, the shortfall in mapping global genetic diversity is an error that his company plans to rectify. Global Gene Corp aims to capture anonymized genetic data from populations and share it with academic and pharmaceutical industry researchers. It will begin by focusing on South Asia, primarily India in the first instance. Although there are issues of data storage and security with the expansion of genetic mapping – a single human genome contains 3 gigabytes of data – a better understanding of the impact of genetic variations on the function of potential drugs, or identifying population–specific targets – could cut the costs of drug development. Moreover, providing more tailored health care to the diverse and growing human population could potentially save millions of lives. "This is the future. Just imagine if we can change the health outcome for every individual – that is a phenomenal promise," said Mr Jamuar. (*BBC*, 22 June 2017)

▶▶ At least 160 people have died, and millions more displaced after heavy monsoon rains caused landslides and flooding across northern India, southern Nepal and Bangladesh. In flooding in Sierra Leone, at least 200 people died in flooding in Freetown, the country's capital. Many of the victims in South Asia had drowned, or were trapped in collapsed houses or underneath toppled trees. According to the aid agency, Heifer International, the heavy rains hit at a particularly bad time for food supplies, just after the planting of rice crops, and large numbers of livestock were swept away. Landslides and flooding are common in south Asia during the summer monsoon season, and widespread deforestation and poor urban planning make it harder for the land to absorb rainfall, worsening the flooding. In India, flood–waters have damaged bridges, power lines and washed away thousands of homes. This has affected at least 2.5 million people, of whom 200 000 are staying in 440 relief camps. In the remote region of Assam, railway lines are flooded, so helicopters are dropping food supplies and water packets to the worst–affected areas. Further westward, in the state of Hamchal Pradesh, soldiers recovered the bodies of 46 people who had been travelling in buses which were buried by a massive landslide. India's wildlife, national parks and endangered species have also been affected by the floods. (*Irish Times*, 14 August 2017)

▶▶ The World Bank estimates that India will become a high–middle income country within the next 30 years, spurred on by economic and tax reforms. The World Bank's Chief Executive Officer, Kristalina Georgieva, praised these reforms, saying that they have had a visible impact on foreign direct investment – which has doubled from US$ 36 billion in 2013–14 to US$ 60 billion. India has also moved sharply up the World Bank's global Ease of Doing Business ranking. Moreover, investment in infrastructure is also fostering economic growth. Over recent years, the country has moved more than 60 million people out of extreme poverty, and has set a target of eliminating extreme poverty by 2026. Mrs Georgieva believes that India could meet this goal by 2022 – well ahead of its target. "What we have seen is remarkable overall success story of India. Extraordinary achievements in the last three decades, the per capita income has quadrupled. It was done with an eye on lifting out people out of poverty," she said. (*Economic Times*, 4 November 2017)

▶▶ A recent study found that out of the 56% of households covered by India's government–funded health care insurance, 66% of these households who sought treatment in public hospitals, and 95% of those who sought treatment in private hospitals, had to pay for treatment. The health care insurance scheme was introduced by the Modi government in 2017, in order to scale–up and strengthen health care insurance, and to purchase services from public, not–for–profit and the private sector. 360 million people (30% of the population) in India are have health care insurance, with government–funded insurance covering 200 million people, with private insurance covering the remainder. One of the main objectives of the expansion of government health insurance was to reduce the number of households facing "catastrophic expenditure" for health care, as an estimated 60 million people each year fall below the poverty line due to health care expenses. However, the results of this study suggest that hospitals are overcharging for their services, coupled with low awareness of entitlement, means that insurance cover often only leads to a discount of expenditure, rather than cashless care. (*The Telegraph*, 23 November 2017)

▶▶ Figures from the World Health Organization (WHO) and published in the World Malaria Report show that 6% of the world's new cases of malaria, and 7% of malaria–related deaths, occur each year in India.

Moreover, it accounts for 90% of cases in Southeast Asia, and the highest number of deaths in the region. According to the report, 85% of estimated vivax malaria cases occurred in just five countries (Afghanistan, Ethiopia, India, Indonesia and Pakistan) – with India having the highest share of cases at 51%, followed by 12% in Pakistan and 10% in Ethiopia. The report also criticised the weakness of India's surveillance system – a significant contribution to India's malaria burden. However, Union Health Minister JP Nadda is optimistic about India's progress in malaria control, tweeting that "India has successfully reduced its new malaria cases by one–third and crossed the malaria mortality targets of 2020." (*Hindustan Times*, 29 November 2017)

▶ The Americas

▶▶ Venezuela's HIV treatment programme was once a model for the developing world, with free, public treatment available since 1999. It imported affordable generic drugs from India, challenged the patent monopolies of Western pharmaceutical companies, and targeted marginalised communities with the distribution of free condoms. However, the country's political and economic crisis has left its once–leading programme in ruins. Hospitals lack the basic drugs to treat infections arising from shortages of antiretroviral drugs, and people living with untreated HIV are developing drug–resistant strains of the virus. Condoms are only available at hugely–expensive private pharmacies, and there is no infant formula milk to give to babies with HIV–positive mothers, to avoid transmission via breast milk. There are no accurate figures for HIV infections – the most reliable suggests that 200 000 people may be infected. However, due to the lack of treatment, people are dying from AIDS at rates reminiscent of the epidemic's early days in the 1980s. The only blood screening in the public health system is at blood banks, and pregnant women are not screened for HIV, so the risk of mother–to–child transmission is high. In 2016, a coalition of Venezuelan people living with HIV asked the Global Fund for help; it was refused because Venezuela is a high–income non OECD country (indeed, it has the world's largest oil reserves, and continues to export petroleum). The government, which denies there is a crisis, may not support their efforts, and there is currently no other organised campaign to bring drugs into the country. (*Globe and Mail*, 21 June 2017)

▶▶ For the first time in US history, the US Food and Drug Administration (FDA) is planning to introduce new regulations on tobacco products as well as on tobacco vaporisers (eg, e–cigarettes). According to the FDA, the policy's aim is to reduce the addictiveness of cigarettes caused by nicotine amongst US smokers, along with the number of consumers, which would eventually lead to a significantly lower amount of tobacco–related deaths and diseases. After the announcement of the new regulatory plan, shares of tobacco companies plunged dramatically – Altria Group by 17%, British American Tobacco's by 11% while Philip Morris International Inc. dropped by 7%. Moreover, the FDA considers tobacco to be the leading cause of preventable death in the US – killing more than 480 000 people each year, and costing US$ 300 billion in health care. The FDA is now turning its attention to flavoured tobacco products, such as menthol. Tobacco companies, such as British American Tobacco (BAT) and Reynolds American Inc, are convinced that "future success will require transformative, innovative products and changing the conversation about tobacco harm reduction." (*BBC*, 28 July 2017)

▶▶ In 2016, more than 60 000 people died from drug overdoses in the USA – higher than gun homicides and road fatalities combined. In October, President Trump declared opioid addiction a public health emergency, opening additional federal assistance for treatment and pledging a crackdown on drug traffickers. Mr Trump's response also included a call for doctors to be educated on the prescription of opioids, and stated that he will urge the Chinese President, Mr Xin Jinping, to take action over China's production of fentanyl, a drug that is infiltrating the USA's heroin supply and exacerbating fatal overdoses. Today's health emergency originated when many people became addicted to prescription opioids over the past 20 years, and switched to heroin when prescription drugs ran out. A public health emergency declaration lasts for 90 days, but can be extended. The government will use the Public Health Service Act to combat the emergency, but there is a funding shortfall and additional funding must be negotiated with lawmakers. (*Washington Times*, 26 October 2017)

▶▶ According to the 2017 School Weight and Height survey, conducted by the Costa Rican Ministries of Health and Education, 34% of the country's school–age children are overweight, a large increase over

previous years. Health officials highlight "drastic changes" in children's nutrition as the driving force behind the change, and longer commutes, busier parents, lack of recreational facilities combined with easy access to junk food also makes life more sedentary. Costa Rica is not alone in the increasing prevalence of obesity, as worldwide an estimated 4.3% of boys and 6.3% of girls were overweight, and in 2015 this had increased to 30.3% of boys and 33.1% of girls. The Costa Rican Social Security Agency is bolstering its health promotion activities, and is launching heart–health programmes and improving heart monitoring services. (*Costa Rica Star*, 14 November 2017)

▶▶ Child marriage was banned in Mexico in 2014, but the country's rates of child marriage have not fallen, despite the ban and falling rates globally. According to UN data, 25% of Mexican women aged 50–54 years says they married as children, compared to 21% of women aged 20–24 years – a small change over a generation. This data also shows that 6.8 million women in Mexico married before the age of 18, and 25% of Mexican women marry under–age. In the region of Coatecas Altas, some women report that the average age of marriage is 14 years. UN Women state that marrying before 18 means that young women are more likely to be poor, have a lower education level, less job opportunities and be victims of domestic violence. There are many drivers behind Mexico's rates of child marriage, but underpinning them is society's perceptions of women, and women's roles. (*NPR Goats and Soda*, 23 November 2017)

▶ The Bill and Melinda Gates Foundation

▶▶ In June, Bill Gates gave US$ 4.6 billion of Microsoft shares to the BMGF, followed by a new campaign to combat the spread of malaria. This latest donation reduces his Microsoft holdings from 2.4% to 1.3% (although Microsoft stock accounts for 9% of his overall net worth, and he remains the world's wealthiest individual, despite donating billions of US$). The anti–malarial campaign focuses on mosquito nets, and is part of the Foundation's wider efforts to defeat malaria. Donated nets will be distributed by World Vision to families in the Inhambane region of Mozambique, where malaria is still prevalent. The Foundation is also seeking to raise public awareness of malaria, and Mr Gates points out that 429 000 people died from the disease in 2016, although there are "miraculous" falls in malaria deaths since 2000, with numbers halving. (*Forbes*, 15 August 2017)

▶▶ The state government of Andhra Pradesh (India) is planning to use drone technology in soil testing, and will hold talks with the BMGF to launch a project to assess soil conditions. The BMGF has implemented a similar project in South Africa, and each project aims to assess soil conditions in differing terrains, to determine the most suitable crops, plus crop monitoring. The drones will survey soils across Andhra Pradesh, and will combine the results with data from soil samples to make recommendations. Experience from earlier projects show that this approach can improve agricultural productivity, and the state government will draw upon the guidance of scientists from overseas and India to implement it. The Chief Minister, Mr N Chandrababu Naidu said "it is a unique experiment that forms a part of the government's endeavor to adapt the latest technologies in the agricultural sector, and it was imperative that the farmers have a reliable database of the diverse soil conditions which have a direct bearing on the yields." (*The Hindu*, 29 August 2017)

▶▶ Over the past few years, there has been remarkable progress in reducing infant and child mortality, reducing extreme poverty, ill health, and deaths during childbirth. However, in a report described as a "wake–up call", the BMGF suggests that progress could be faltering, and that campaigns to eradicate extreme poverty, HIV and malaria are going awry, and this is going unnoticed. This is partly due to demography, as most chaotic countries have high birth rates, and huge fertility gaps have opened between failing states and the rest of the world – and high birth rates place huge strains on working–age populations. Deep poverty is drying up in South Asia, but the falling numbers of people in extreme poverty in sub–Saharan Africa do not outweigh population growth, so overall numbers remain constant. There are risks that HIV infections will rebound, due to complacency over new treatments, and progress in reducing malaria infections may be halted by the rise of drug–resistant parasites. Mr Gates is also concerned that high–income countries may slash their aid expenditure. Despite these real worries, there is room for optimism – better domestic policies could boost well–being without massively increasing expenditure, birth rates may fall faster than expected, and medical breakthroughs could lead to improved treatments. Indeed, the overall value of the report lies more in its estimates of what is at stake if progress stalls – between the most optimistic and pessimistic scenarios lie the lives and well–being of millions of people – and in identifying the largest risks to progress. (*Economist*, 14 September 2017)

▶▶ Immunocore, a UK–based pharmaceutical company, has received US$ 40 million investment from the BMGF to help develop immunotherapies for infectious diseases, ahead of what is expected to be a much larger funding round. To date, Immunocore has concentrated on applying its T–cell receptor (TCR) technology to treat cancer, but the new investment will extend its reach to fighting infections, starting with HIV and TB. The company's TCR works by stripping off T–cells receptors, and engineering them to become drugs in their own rights. Dr Chris Karp, the BMGF director of discovery and translational science, said that directing these TCRs against pathogens could treat intractable infections far more effectively than existing drugs. The company emphasises that much more pre–clinical work was needed before the new treatments are ready to test in patients, and if the development goes well, the BMGF would consider further funding, either through grants or equity investment. (*Financial Times*, 17 September 2017)

▶▶ Africa's Academy of Science (AAS) has announced an open–access publishing platform – AAS Open Research – the first platform exclusively for African scientists. It will publish articles, research protocols, data sets and codes, mainly within days of submission and before peer review (papers will be indexed after they pass review). The platform is being created by the open–access publisher F1000, and although

other open–access publishers already focus on Africa, it is the first to adopt open peer review. It will initially be limited to submissions from AAS fellows and affiliates, as well as researchers funded through programmes affiliated to the Alliance for Accelerating Excellence in Africa; however AAS has a longer–term goal of opening the platform to more researchers. The publication fees (US$ 160 – 1100 per article) will be met by grant funders. Some scientists are concerned that these platforms might hinder African scientists' career progression if they are not publishing in conventional journals (eg, in South Africa, researchers are rewarded for publishing in journals approved by the country's Higher Education department). This venture follows a series of open publishing portals launched with F1000 in the past 18 months, including those funded by the Wellcome Trust and the BMGF. (*Nature*, 15 November 2017)

The GAVI Alliance

▸▸ Thanks in part to its vast and diverse geography, India faces particular challenges in reaching the poorest and most vulnerable groups with its ambitious vaccination programme, which aims to immunise 156 million people a year. To help overcome these obstacles, India's government has launched an electronic vaccine intelligence network – eVIN – which is a smart, easy–to–use technology that provides real–time information on vaccine stocks and flows, so that health officials can make quick and informed decisions. It is a cloud–based and mobile application that allows cold–chain handlers to update information on vaccine stocks after each immunisation session. These updates are stored on a cloud server that gives health officials immediate information on stocks and flows, helping them to adjust levels, reduce wastage and empower health workers. eVIN is implemented in collaboration with the UN Development Programme, and its development was financed by GAVI. (*Devex*, 17 July 2017)

▸▸ Pfizer Inc had made its pneumonia vaccine, Prevanar 13, available at discounted prices to GAVI, where 50 countries are eligible to procure it. However, India has granted a patent to Pfizer, raising concerns that Prevanar 13 would become inaccessible to many in low–income countries. This decision also prevents other companies from making cheaper copies of the vaccine to sell elsewhere, and allows exclusive rights for Pfizer to sell it in India until 2026. The decision by India's patent court comes at a time of ongoing pressure from the USA for India to tighten its patent laws. Following criticism over the high price of Prevanar 13, Pfizer had reduced the price to NGOs in 2017, but has welcomed the granting of the patent, saying that Prevanar 13 took 2.5 years to develop, and has been available in India since 2010. In 2016, Médecins Sans Frontières filed an objection to Pfizer's patent application, arguing that a patent would deprive many developing countries of cheaper copies, and is considering its legal options. At least one Indian company is considering a post–grant opposition. (*Reuters*, 22 August 2017)

▸▸ Cholera is mainly a disease of poverty, preying especially on vulnerable communities in areas with poor sanitation. Each year, 95 000 people die as a results of cholera, many of them children. In 2017, cholera spread at an unprecedented rate in Yemen – where more than 2000 people have died as a result – and there are ongoing outbreaks in Somalia, South Sudan, Haiti and other countries across sub–Saharan Africa and Asia. Cholera is entirely preventable, and the WHO has pledged to end it by 2030. Cholera has to be tackled with a multi–sectoral approach: investments in water, sanitation and hygiene are essential; alongside easy access to treatments such as oral rehydration solutions and intravenous fluids, and the proactive use of oral cholera vaccines. The WHO maintains a global stockpile of cholera vaccines, with support from GAVI, and more than 15 million doses have been distributed to 18 countries since the programme's inception in 2013. In 2018, the stockpile will increase to 25 million – a huge increase from its original 2 million base. (*Irish Examiner*, 11 October 2017)

▸▸ Ahead of the meeting of GAVI's board of directors, Médecins Sans Frontières (MSF) has called on GAVI to ensure the sustainable access to immunisations by putting children's health at the centre of its funding model, highlighting how nearly 1–in–10 children worldwide do not receive any vaccinations. MSF states that GAVI support is solely assessed on a country's Gross National Income per capita (GNI), with a current threshold of US$ 1580. Once this threshold is reached, GAVI support is withdrawn over a 5–year period, and the country is expected to increase domestic funding for immunisation, eventually reaching of funding. By the end of 2020, 20 countries will have lost all GAVI funding, 16 countries will have lost

funding by the end of 2017, and 8 countries have already lost funding. However, some of the countries scheduled to lose GAVI support have poor or declining immunisation coverage, and the board meeting will consider plans to support their transition. MSF calls on GAVI to strengthen its funding model, by factoring in measures of immunisation coverage, and not rely solely on economic criteria. (*ReliefWeb*, 28 November 2017)

▶▶ GAVI has agreed US$ 85 million of funding towards the bulk–buying and introduction of typhoid vaccines in low–income countries. GAVI said that it expects the first countries to apply for the vaccine in 2018, and aims to roll it out further in 2019 for children aged over 6 months. Typhoid is a serious – often deadly – disease caused by consuming contaminated food or water, affecting 12–20 million people worldwide each year. 126 000 people died from the disease in 2016, and those who survive become chronic carriers of the disease. Although typhoid is treatable with antibiotics, access to these drugs is limited in low–income countries, and there are increasing prevalence of drug–resistant bacteria. Indeed, GAVI's chief, Mr Seth Berkeley says that the growing spread of drug resistant strains of typhoid posed a major threat, to which a vaccine could a valuable defence. "Strong coverage through immunisation together with efforts to improve access to clean water and hygiene will play a key role in dramatically reducing the disease," he said. (*Reuters*, 30 November 2017))

▶ The World Bank

▶▶ The World Bank has launched the first pandemic emergency financing instrument, or "pandemic bond", for epidemics. It will support emergency financing to rapidly fight counteract future health crises, such as the Ebola outbreak in 2014. Mr Michael Burnett of the World Bank, noted that if this instrument had been available in 2014, US$ 100 million could have been mobilised early in the Ebola outbreak. The instrument will offer coverage to all countries eligible for support from the International Development Agency, and payments will depend on the size of disease outbreak, growth rate and the number of countries affected. According to Mr Bennett, it will provide more than US$ 500 million of coverage against pandemics over the next 5 years, against infectious diseases such as pandemic influenza strains, filoviruses, plus others such as Rift Valley Fever and Lassa fever. The World Bank will pay bondholders the equivalent of the insurance premium plus a funding spread, in return for a payout if the bond is triggered, and was oversubscribed by 200% at its launch. Pandemics are the most likely uninsured risk to incur, and the World Bank estimated that the annual global cost of moderately severe to severe pandemics is estimated at approximately US$570 billion – 0.7% of global GDP. (*Reuters*, 28 June 2017)

▶▶ According to a study from the World Bank, the food produce destroyed by drought would feed 80 million people a year, noting that whilst flooding and storms have an immediate impact on food supplies, droughts are slower–acting. Problems caused by droughts are passed onto the next generation, as women born during droughts have less access to education, have more children and are more likely to suffer from domestic violence. When crop yields fall during droughts, farmers can be forced to cultivate forests – and deforestation can further decrease water supply and exacerbate climate change. The World Bank said many countries affected by drought are overlapped with areas with large food shortages and are classified as fragile, intensifying the need to tackle the problem. It recommends constructing new water storage and management infrastructure, combined with measures to control demand for water, safety nets to help families cope with the economic consequences of drought, and incentivise utility companies to invest and improve their water efficiency. (*The Guardian*, 24 October 2017)

▶▶ The World Bank defines extreme poverty as living on US$ 1.90/d or less – mostly spent on food, which may be insufficient to ward off hunger or malnourishment. At this level of income, housing will usually be inadequate, and in the absence of free education or health care, insufficient to cover school fees or health expenses. Whilst millions of people in extreme poverty live in low–income countries, more than 50% live in middle–income countries like India, Nigeria and China. However, wealthier countries have higher poverty lines, whilst low–income countries have lower poverty lines. This has led to the World Bank setting "poverty line" figures for middle–income countries: US$ 3.20/d for lower middle–income countries (eg, Egypt and the Phillippines), and US$ 5.50/d for upper middle–income countries (eg, Brazil, Jamaica and South Africa) – and, US$ 21.70/d for high–income countries. These new standards give

a benchmark to measure progress in poverty reduction, and for middle–income countries to assess their progress. The UN has pledged to end extreme poverty by 2030, and the poverty lines remind us that although extreme poverty is falling, deep, intractable pockets remain. (*NPR*, 25 October 2017)

▶▶ According to the International Monetary Fund (IMF), the median level of government debt in sub–Saharan Africa will probably rise to 50% of GDP in 2017, from its current level of 34%. The increase is due to slow economic growth, falling commodity prices, widening fiscal deficits, depreciating currencies, and is increasing pressure on SSA's financial sector and limiting its potential for stimulating economic growth. The number of low–income countries in debt distress, or facing a high risk of debt distress increased from 7 in 2013 to 12 in 2016, and several countries have had their credit ratings downgraded. "High levels of public debt can be quite harmful," said the Director of IMF's Africa Department, Abebe Selassie. "The debt–servicing cost can be a major source of drain of resources that could otherwise be used." (*Bloomberg*, 30 October 2017)

▶▶ The International Monetary Fund's (IMF) latest *World Economic Outlook* predict a year of healthy economic growth in 2018 for the global economy, with low levels of market volatility. In September 2018, central banks may curtail or stop bond purchase programmes which were established to drive down interest rates and provide economic stimulation. For several years, the IMF has reported below–trend economic growth, but now says that "the global upswing in economic growth is strengthening." The US economy is predicted to grow by 2.5% in 2018, China by 6.4%, Japan by 0.9% and Germany by 1.6%, although the IMF points to "lacklustre" growth in many nations of sub–Saharan Africa, the Middle East and Latin America, and wealthy economies may be affected by wage stagnation. Stronger economic performance is based on confident consumers and companies investing in resources, and is not dependent on a particular region or sector; and it places the world in a better position to deal with the next economic downturn. Policymakers can now start to focus on normalising interest rates and repairing their national finances. Moreover, economies – to date – have been resilient in the face of uncertainty, with South Korea remaining prosperous in the face of threats from North Korea, corporate scandals and warnings from the US President that their free–trade agreement might not survive; and the UK economy continues to growth despite uncertainty over its exit from the European Union. One concern for the global economy as a whole is that recovery has been built on too much debt, which companies will struggle to service when growth eventually weakens. (*Bloomberg*, 2 November 2017)

▶ United Nations

▶▶ Following violence against Rohingya Muslims in Myanmar, Nikki Haley, the US ambassador to the UN, has called for countries to suspend weapons provision to Myanmar until the military puts sufficient accountability measures in place. The UN has accused Myanmar's government of ethnic cleansing, following the displacement of hundreds of thousands of people in Rakhine State, and Nikki Haley's statement was the first time that the USA has supported the UN's position. However, China and Russia have both endorsed Myanmar's government, and Myanmar itself rejects the accusations and has denounced rights abuses. Thang Tun, Myanmar's national security adviser, told the UN that there was no ethnic cleansing or genocide, and that the country has invited UN Secretary General Antonio Guterres to visit. To date, the Trump administration has mostly followed the Obama policy of forging closer relationship with Myanmar, partly to counter China's growing influence. Aid groups have urged free access to Rakhine, where more than 500 000 people have fled to Bangladesh, but hundreds of thousands of those remaining are cut off from food, shelter and medical care – since the insurgency attacks in August, the Myanmar government has prevented aid groups and the UN from working in the northern part of Rakhine. Despite the Myanmar Red Cross co–ordinating aid in the state, the International Red Cross fears insufficient aid is reaching people. (*Reuters*, 28 September 2017)

▶▶ Mark Lowcock, the UN humanitarian chief, told the Security Council that more than 13 million people inside Syria still need humanitarian assistance, and nearly 50% are in "acute need", having fled their homes due to hostilities and with little access to food, health care and other basic needs. He also said that the number of internally–displaced Syrian people fell from 6.3 million to 6.1 million, although levels of new displacement remain high – 1.8 million people between January and September 2017. Moreover,

nearly 3 million people remain in besieged or hard–to–reach areas, where the UN faces "considerable challenges" in meeting humanitarian needs. Mr Lowcock said that progress in de–escalating the conflict had not yet led to increased humanitarian access; indeed, recent airstrikes on Al Mayaldin has left medical facilities "inoperable", heavy fighting and airstrikes continue to cause civilian deaths and casualties in the province of Deir el–Zour, and fighting in the city of Raqqa had resulted in 436 000 people being displaced. The UK's UN ambassador, Matthew Rycroft, called the situation in estern Ghouta "atrocious", and that de–escalation should not mean bombardment. "What we fear is that the de–escalation zone is becoming a starvation zone. So we call on the Syrian regime and their allies to lift the blockade to allow humanitarian aid to get through," he said. (*Voice of America*, 30 October 2017)

▶▶ The UN has described the health care available for refugees at a detention centre on Papua New Guinea's Manus Island has "inadequate", which 600 refugees are refusing to leave despite essential services being cut off. They are under pressure to relocate to a nearby transit centre. In November a 38–year old refugee with a known heart condition collapsed at a detention centre, and as the island is without ambulance services, a passing car had to be flagged down to take the man to the island's medical centre. According to sources, the man was not treated at the medical centre as it lacked the necessary equipment, and was sent back to the detention centre. The refugee claims that a drunk security guard prevented him from being visited by staff from the UN refugee agency. Nai Jit Lam, the UN deputy director for the region's refugees, recently visited the centre, and found that the health care services for refugees had been downgraded. "Many of the refugee population have medical and mental health issues as well which need constant monitoring and constant attention," he said. Refugees have also reported that the detention centre's sewer had backed–up, as its pumps were unable to function when the electrical generators were removed. (*Radio NZ*, 6 November 2017)

▶▶ The UN World Food Programme (WFP) is trialling Distributed Ledger Technology ("blockchain") to make delivering food assistance faster, more secure, cheaper, and to reach as many people as possible. Under its pilot scheme, Building Blocks, 10 000 refugees in Jordan's Azraq camp can pay for their food supplies by means of an entitlement recorded on a blockchain–based computing platform. The WFP believes that full implementation of blockchain technology could lead to significant cost savings, potentially millions of US$ each year. Moreover, at November's Humanitarian Blockchain Summit (organised by the Institute of Humanitarian Affairs, Fordham University and the UN), an initiative to combat child–trafficking was announced, which will use blockchain technology to register undocumented children. (*Nasdaq*, 17 November 2017)

▶▶ The UN and other international agencies have warned that thousands of Yemeni people could die each day if the Saudi Arabia–led coalition does not lift its blockades on Yemen's ports. On 6 November, the coalition closed all air, land and sea access to Yemen, following the interception of a missile fired towards Riyadh, saying that the flow of arms from Iran to its Houthi opponents in the the Yemen war had to be stemmed. The UN has appealed for the blockage to be lifted, saying that it could spark the largest famine the world has seen in decades – and 7 million people are already on the brink of famine in Yemen. The UN also reported that the closure of Yemen's border has halted the delivery of emergency assistance for nearly 280 000 internally–displaced people. In a joint statement, the heads of the World Food Programme, UNICEF and the WHO said that unless all ports are re–opened, Yemen's 7 million people at risk of famine could grow by 3.2 million. Moreover, at least 1 million children are at risk if a fast–spreading diphtheria outbreak is not halted, and the lives of 400 000 pregnant women and their babies are threatened by a shortage of drugs. The UN refugee agency is also alarmed over the deteriorating humanitarian situation, saying that at a centre for displaced Yemenis in Sanaa "hundreds more people are approaching the facility daily, saying they are no longer able to meet basic needs or afford medical care." (*Hindustan Times*, 22 November 2017)

▶ UN AIDS and The Global Fund

▶▶ According to UNAIDS, tuberculosis (TB) is one of the most common causes of death amongst HIV–positive people, causing about 33% of AIDS–related deaths in 2015. Rwanda, which has a reported HIV prevalence rate of 3% – with 6.3% in Kigali – is piloting the early screening for TB amongst people living with HIV in Kigali. This pilot phase will cover about 30% of people infected with TB in Rwanda. Currently, most HIV–positive people only go for screening after symptoms appear, but treatment is more successful if started early. The pilot will be rolled out across Rwanda's 18 districts, targeting six health centres in each district. Each health centre will have a Peer Educator who will mobilise people living with HIV to attend screening, and screening should target the general public, including prisoners, children aged under 15 and adults aged over 55, who all have higher risks of TB infection. Dr Betru Woldesemayat, the UNAIDS country director for Rwanda said "the initiative to focus on Kigali City will contribute to advancing of the Fast Track agenda in the cities where HIV prevalence is much higher." He also noted that a strengthened contribution of civil society organisations to finding a combined solution will have a positive impact on the population. (*New Times Rwanda*, 23 June 2017)

▶▶ The latest report on the HIV pandemic from UNAIDS shows that that the number of HIV–positive people receiving treatment has reached a record 19.5 million – out of a total of 36.5 million people living with HIV. Moreover, AIDS–related deaths have fallen by nearly 50% since their peak of 1.9 million death in 2005. Sub–Saharan Africa, which has been hit particularly hard by the HIV pandemic is showing encouraging progress, with new HIV infections falling by nearly 30% in eastern and southern Africa (with a related 10–year increase in average life expectancy); and Malawi, Mozambique, Uganda and Zimbabwe have cut new infections by 40% or more since 2010. Despite progress in sub–Saharan Africa, the Middle East/North Africa, and Eastern Europe/Central Asia, AIDS–related deaths have risen by 48% and 38% respectively, mainly because many HIV–positive people lack access to treatment, although the report notes that some countries in those regions who have taken concerted action against HIV have seen better results, eg, Algeria, Morocco and Belarus. Overall, the report found that whilst HIV infections are falling, they are not falling quickly enough to reach global targets, and that that "around 30% of people living with HIV still do not know their HIV status, 17.1 million people living with HIV do not have access to antiretroviral therapy and more than half of all people living with HIV are not virally suppressed." (*Al Jazeera*, 20 July 2017)

▶▶ Mr Peter A Sands, a former chief executive of Standard Chartered Bank, was chosen as the new head of the Global Fund. Since its inception 15 years ago, the Global Fund has struggled to raise enough funds to fulfill its mission of combatting HIV, malaria and TB. When it launched in 2002, it was envisaged that the Global Fund would raise and spend at least US$ 8 billion annually, but thanks to funding cutbacks it has struggled to raise US$ 4 billion each year. However, thanks to falls in the prices of generic drugs, the Global Fund has claimed to have saved 22 million lives in the developing world, helping 11 million and 7 million people access HIV and TB drugs respectively. After accusations that it was becoming a swollen bureaucracy and that it was enabling aid recipients to pilfer funds, its most recent chief, Dr Mark R Dybul, has been credited with making it more effective and efficient; and in 2016 it was only 1 of only 3 multilateral agencies to earn top marks for "value for money" from the UK's Department for International Development's score–card. Mr Sands stated that he hopes to have "elimination of the three diseases as epidemics firmly in sight" during his term, which ends in 2022. He also said that it would be "premature" for him to outline any changes he plans to make, and could not name any countries that could act as model aid recipients. (*New York Times*, 14 November 2017)

▶▶ The AIDS Healthcare Foundation (AHF), the largest non–profit HIV organisation providing HIV care to more than 833 000 people in 39 countries worldwide, has called on the Global Fund to end the use of per capita Gross National Income (GNI) as part of the Global Fund's grant eligibility criteria. Currently, eligibility is based on a country's World Bank lending group classification – which is tied to its GNI – and on its HIV prevalence rate as a proxy for disease burden. If a country's per capita GNI exceeds US$ 3955, it is designated as an upper–middle income country (UMIC) and if it does not have a high burden of disease, it becomes ineligible for support from the Global Fund. Support can be withdrawn even if HIV prevalence is increasing – and the AHF argues that the Fund's "Transition Readiness Assessment Tool", which considers the capacity of UMICs to sustain HIV programmes, does not take into account any in-

creases in new HIV infections. Dr Jorge Saaverdra of AHF says "right now, a developing country can be cut off from support even if the rate of new HIV infections is skyrocketing and its epidemic is not under control." The AHF has been spearheading a campaign to change how the World Bank classifies middle–income countries – currently, a country is classified as middle–income if it has per capita GNI US$ 2.76/d – barely above the International Poverty Line of US$ 1.90/d. Instead, the AHF calls for the World Bank to set the middle–income category at the equivalent of US$ 10/d. This would increase those countries' access to foreign aid, including HIV drugs and other essential medicines. (*InDepth News*, 26 November 2017)

▶▶ A UNAIDS report published on the 2017 World AIDS Day shows than more men than women are dying from AIDS, despite more women than men being HIV–positive. This is because overall fewer men are tested for the virus, or have access to treatment. The situation is particularly acute in sub–Saharan Africa, where boys and men living with HIV are 20% less likely than HIV–positive girls and women to know their status – and people who are not receiving treatment are more likely to transmit the virus. Moreover, men are more likely to adhere less strictly to their treatment regime, leading to 58% of AIDS–related deaths occurring amongst men, despite the lower prevalence. The report finds than many men refrain from testing because they fear stigmatisation, and are less likely to visit health care facilities so are less likely to be diagnosed with life–threatening conditions. (*Voice of America*, 1 December 2017))

▶ UNICEF

▶▶ UNICEF has warned that renewed fighting in the Central African Republic (CAR) has led to increasing numbers of violent acts against children, including murders, abductions, rape and recruitment into armed groups. The true number of incidents is likely to be much higher than officially reported figures, because humanitarian access is severely limited in many areas due to fighting. In addition to the many brutalities reported, the intensification of violent conflict has resulted in thousands of children being denied their most basic rights to education and health. It is estimated that 94 000 primary school–children could not take their end–of–term examinations because of school closures. Looting by armed groups has caused the closure of many health centres, stopping essential care and routine immunisations for children. "Children in CAR have suffered disproportionately from the waves of violence that have swept the country over the past three years. Armed groups and parties to the conflict must cease these flagrant violations of children's rights and make every effort to keep children safe," said Christine Muhigana, the UNICEF representative for CAR. (*Newswire Canada*, 18 July 2017)

▶▶ According to UNICEF, more than 700 million women were married as children – and India alone is home to a third of the world's child brides, putting it amongst countries with the highest prevalence of child marriages in the world. Despite legal restrictions, the practice of young women marring before their 18th birthday – with the authorities often turning a blind eye – still has much support from Indian society. Even though child marriage is more likely to happen in rural than urban areas, a recent study proved that the practice is not mainly a rural occurrence with nearly 1–in–4 girls being married in rural areas in comparison to 1–in–5 girls in city areas. Furthermore, child marriage affects both girls and boys, but the impact on girls is much greater – leading to devastating consequences such as low female literacy rates, exploitation, sexual violence, domestic abuse, and death in childbirth. Ending child marriage requires the engagement of religious and cultural institutions but also the awakening of boys and men's consciousness in "getting the message out, using social media and school text books, and starting from a young age," says charity ActionAid. (*Reuters*, 21 July 2017)

▶▶ Ratul Narain, a graduate from Stanford University, has invented a small bracelet which is fitted to premature babies, and sounds an alarm if the baby's temperature falls below 36.5°C, prompting intervention and treatment. It is manufactured by Bempu Health in Bengaluru, and has been recognised as one of the 25 best innovations in 2017 by TIME magazine. About 10 000 bracelets have been used world–wide (including Pakistan, Papau New Guinea, Togo and Ghana), via UNICEF initiatives. In India, 1–in–3 newborn babies are of low birthweight, or weight less than 2.5 kg, compared to 1–in–12 in developed countries. Before developing the device, Ratul spent a year in various hospitals to understand neonatal complications. "Among babies with low birth weight, infections can occur at home. Up to 15% of low–

weight newborns discharged from government NICU would die at home due to complications like infections and hypothermia. The significant cost of facility care for the baby was, therefore, lost at home. That's what made me work on a low–cost solution," said Ratul. (*Times of India*, 27 November 2017)

▶▶ UNICEF has warned that there is little progress in halting HIV amongst children, with 18 children every hour being infected with the virus in 2016. If this trend continues, there will be 3.5 million new cases of HIV infection amongst adolescents by 2030. Worldwide, nearly 37 million people are living with HIV, and this includes 2.1 million adolescents – a 30% increase from 2005. In 2016, 55 000 adolescents and 120 000 children died from AIDS–related causes. HIV–positive children aged under 4 years have the highest risk of dying from AIDS–related causes. UNICEF states that that nearly all the adolescent deaths were in sub–Saharan Africa, and that more girls than boys are infected. The testing and treatment of babies is also falling behind, with less than 50% of HIV–exposed infants being testing in the first 2 months of life. UNICEF confirmed progress on arresting mother–to–child transmission of HIV, with 2 million new infections being averted since 2000, but said that progress was slowing. UNICEF calls for an array of actions, including the treatment of all infected children, and prioritising interventions for adolescent girls in sub–Saharan Africa. "It is unacceptable that we continue to see so many children dying from AIDS and so little progress made to protect adolescents from new HIV infections," said Dr Chewe Luo, head of HIV at UNICEF. (*Voice of America*, 27 November 2017)

▶▶ Libya's Man–Made River (MMR) authority, the international community and UNICEF have been working together to ensure the functioning of Libya's water system. This is following attacks on the Hasawanah reservoir (which serves Tripoli) by a Brak Al–Sharti–based group who are demanding the release of its leader, Mabrouk Ahnish. Mr Anhish is being held in prison by Rada forces. This is the second time in two months that the group have closed the water system. However, the water system has now been reopened and the reservoir is slowly refilling – according to the MMR, it will take 3 more days for water levels to return to normal. The closure of the water system meant that 2 million Libyan people, including 600 000 children in Tripoli and its surrounding areas, were left without running water. This forced people to resort to potentially unsafe or contaminated water, increasing the risks of disease outbreak and adding to the suffering of Libyan children. "Access to water is a fundamental human right and international humanitarian law protects civilian infrastructure and the rights of civilians to access basic services," said Mr Abdel–Rahman Ghandour, the UNICEF special representative for Libya. (*Libya Herald*, 3 December 2017)

▶ World Health Organization (WHO)

▶▶ According to the WHO, expanded access to Community Health Workers – a core component of primary health care – could prevent up to 3 million deaths per year. This could result in an economic rate of return on investment of 10–to–1 in sub–Saharan Africa, but primary health care remains the most underfunded, and commonly overlooked, area of health care. Primary health care also delivers vital maternal objections that would remain unmet in areas with limited or no access to mid–level care. Toyin Ojora Saraki, founder of the Well–being Foundation Africa, argues that the absence of established institutions and infrastructure, combined with chronic funding shortfalls, means that primary health care is often the only form of care in many developing countries. She argued that it can reduce inequalities, thanks to the grass–roots provision of care, and investing in primary health care would have a greater impact on the world's poorest people, compared to investing in mid–level care. She highlights barriers to extending primary health care, including lack of resources and government commitment to driving ti forward, and calls for greater focus on improving the quality of primary health care services around the world, and that without effective monitoring systems, there is little incentive to make improvements. (*Huffington Post*, 9 August 2017)

▶▶ Following global condemnation, WHO's Director General, Tedros Ghebreyesus has rescinded the Zimbabwean President, Mr Robert Mugabe's, appointment as a WHO "goodwill ambassador". According to the campaigning group, Human Rights Watch, the appointment "embarrasses" the WHO and its leadership, and the US State Department said that it "clearly contradicts the United Nations ideals of respect for human rights and human dignity". The *New York Times* highlighted in 2009 how Mr Mugabe's regime had wrecked Zimbabwe's health care system, leading to cholera and the spread of other diseases. Indeed, the international response centred on one point – can some–one be a goodwill ambassador if they are

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widely regarded as a violent, tyrannical despot? Zimbabwe's government confirmed that it respected the WHO's decision to withdraw Mr Mugabe's appointment, but noted that Mr Mugabe has already contributed hugely to the world's fight against non–communicable diseases. (*Washington Post*, 22 October 2017)

▶▶ According to a report from Results UK, an advocacy organisation that works to influence political decisions on health, education and economic opportunity, officials are overlooking a new, potential problem as the eradication of polio grows nearer. The Global Polio Eradication Initiative and the US$1 billion it channels each year into the WHO is already being wound–down – funding is due to be halved by 2019, and will cease thereafter, except in countries that are still battling polio or at high risk of its return. This could severely undermine low–income countries' efforts to continue to vaccinate against polio and other diseases, such as measles and rotavirus, plus damaging the surveillance network needed to ensure that the disease is truly gone – 70% of surveillance funding comes from this initiative. The end of the polio programme could place substantial financial pressure on the WHO, which receives 25% of its funding from the polio campaign, and the report also raises the alarm over the state of planning for the end of the polio eradication effort. The WHO raised its "great concern" on its reliance on this funding at the May World Health Assembly, and the risk to its capacity to deliver key programme areas and to maintain essential ongoing functions. The polio vaccine is currently administered orally, but it will be replaced by an injectable vaccine, and the WHO recommends the use of injectable vaccines for at least a decade after eradication. However, injectable vaccines must be given by trained health care workers, and requires different delivery models – which must be more conducive to the delivery of other childhood vaccines. However, the winding down of the polio eradication effort could give an opportunity to refocus efforts on ensuring that countries have the systems and capacity to vaccinate all children with the 11 WHO–recommended vaccines, but without the necessary planning, the opportunity could be lost. (*STAT*, 13 November 2017)

▶▶ The WHO and member countries has a target of cutting tuberculosis deaths by 95%, a 90% reduction in new cases, and to "ensure that no family is burdened with catastrophic expenses due to TB." However, Médecins Sans Frontières (MSF) has expressed grave concerns over South Africa's ability to reach these targets. Tackling TB in South Africa is a global concern, as its high HIV incidence predisposes people to TB, and its increasing rate of drug–resistant TB. South Africa has seen falling death rates from TB since scaling–up access to drugs effective against drug–resistant TB – in particular, bedaquiline – although there is general agreement that drug treatments are not enough to tackle the problem of TB. Dr Fareed Abdullah, director for AIDS and TB Research at the Medical Research Council, calls for improved diagnostic tests, agreeing that 100–150 000 TB cases are missed each year in South Africa, and 4 million globally. Improved screening of each patient's contacts is also needed, and South Africa has missed many opportunities for prevention, eg, by not administering drugs to prevent infection from developing into active illness in children. His main hope for combatting TB lies with a new vaccine, and that if the world is to end TB by 2035 "we require new tools and investments to do it." (*Daily Maverick*, 20 November 2017)

▶ Demography

▶▶ India's government plans to replace tax identification cards, known as Permanent Account Number (PAN) cards, with a biometric–based personal identification number (Aadhaar) have been dealt a blow by the country's top court. The court ruled that tax–payers who had opted out of getting an Aadhaar number should not be forced to get one, meaning that they are not yet mandatory to file tax returns. The government argues that PAN cards are easy to fake, and that a person can get several PAN cards. However, critics say that the government cannot forcibly take people's biometric details, and have raised concerns over the security of the world's largest biometric database, which has already been affected by a number of leaks of citizens' records. Over the past 8 years, the Indian government has collected fingerprints and iris scans from more than 1 billion residents – nearly 90% of the population – and stored them in a high–security digital centre, and each person was provided with a randomly–generated, unique 12–digit identity number. It has been using Aadhaar to transfer government pensions, scholarships, wages for a jobs–for–work scheme and benefits for cooking fuel to recipients, as well as to distribute cheap food to poorer people. (*BBC*, 6 June 2017)

▶▶ Soybeans are likely to replace corn as the most widely sown crop in the USA, and soybeans harvests are also increasing in Brazil and Argentina. The rise of soybean harvests is due to China's trebling its soybean imports over the past 10 years, to an estimated 93 million tonnes – and imports increased even as its imports of other industrial commodities have fluctuated. The global demand for wheat (increasing 1% each year) is in line with population growth, but soybean demand has risen by 5% each year. The bulk of this growth is due to its use in animal foodstuffs – soybeans are high in protein and livestock fed on it fatten quickly – and it is the only plant protein with complete amino acids. To meet the rising demand, animal husbandry in China is changing from small–scale operations where food scraps are fed to pigs, to industrial businesses. Meat consumption in China is rapidly rising, driven by a growing urban population – increasing by 20 million every year – which tends to eat more meat. (*Financial Times*, 20 June 2017)

▶▶ According to a report by UNESCO, the UN education agency, statistics on the global access to education could be wrong by up to 350 million children – equivalent to the combined populations of the UK, Germany, Frank, Italy and Spain. These "invisible" children are typically growing up as "the poorest of the poor" in places unreached by census–takers and administrators. These unregistered people may live in city slums in developing countries, or in families living illegally as migrants. Conventional means of gathering population information – eg, surveys, censuses and records – are only accurate for settled people accessing services. The report highlights how holding governments accountable for delivering education depends on knowing how many people need to be supported; and global goals for reducing illiteracy and increasing access to school must recognise that some of the world's poorest people are not even part of the target. It also warns that education has received a decreasing share of aid budgets – when UNICEF recently reported that there has been "nearly zero progress" on improving access to school in the world's poorest countries over the past 10 years. This is only worsened by a "staggering" problem in teaching quality, with more than 600 million young people who have attended school but lack basic literacy and numeracy skills. (*Reuters*, 6 September 2017)

▶▶ By 2050, 70% of the world's population will live in cities – including 1 billion people in China, 875 million people in India, and 365 million people in the Americas. This mass migration will mean that urban areas have to be capable of handling energy, transport, housing, economic growth etc. Moreover, large urban areas bring together people with different languages, backgrounds and cultures, leading to potential clashes, crime and terrorism. Darrell M West and Daniel Bernstein have examined how digital technology, mobile networks and integrated solutions have helped 17 cities worldwide to manage public safety and law enforcement. The cities under study range from Jakarta, Kuwait, Abuja, Bogota, London and Riyadh, and were chosen to because of geographic diversity, population size and capital city status. They found that the cities that have implemented and adopted best practice in digital technology have a clear vision, financial resources and strong infrastructures, generating positive safety outcomes. They recommend increased resources for digital infrastructure investments, implementing integrated command centres, building public support, using crowd–sourcing platforms to encourage citizen participation, breaking down organisational stovepipes through technology, using police body and CCTV cameras to improve accountability, making data openly available and deploying data analytics, and balancing privacy and security concerns. (*Brookings Institute*, 23 October 2017)

▸▸ Japan is set to become the world's first "ultra–aged" country, with more than 28% of its population aged over 65 years. Currently 27.3% of Japan's population is aged over 65 years, and this is expected to reach 37.7% in 2050. However, poverty amongst older people is an increasing problem, and may be behind the high levels of criminal activity seen in people aged over 65 years. Most criminals in this age group are charged with petty crimes – eg, shoplifting and theft, and this may be underpinned by economic hardship experienced by people aged over 65 years. This group is also more likely to re–offend, with nearly 25% being re–arrested within 2 years of release, compared to 10% for offenders aged up to 29 years. Japan's austere prison conditions – including no talking whilst at work, inmates being obliged to walk in single files, and restrictions on bathing – is not acting as a deterrent to the increasing re–offending rates amongst this group. The situation has become so severe that the government has approved a plan to deploy nursing care staff to about 50% of Japan's prisons, from April onwards. (*Japan Times*, 18 November 2017

▸ Economy

▸▸ Since the 1990s, North Africa has suffered from competition from east Europe and Southeast Asia – both sources of cheap and skilled labour – hampering its efforts to expand its manufacturing base beyond the textiles, mechanical, electrical and cement sectors, and to become a cheap production base for European industry. However, rising wages in east Europe are encouraging companies to shift production in the labour–intensive parts of their supply chains elsewhere, and some countries, such as Morocco, have made gains in new industrial sectors. Now economists are questioning if the region can emulate the Asian "flying geese", where industrial production shifted from mature economies such as Japan towards emerging economies (initially South Korea, Taiwan, Singapore and Hong Kong, then latterly Malaysia, Indonesia, Thailand etc), due to the product cycle, lower labour costs, and state invention. Now, North African countries are eyeing the same path, due to their low labour costs, improving physical and human capital and supportive industrial policies. These countries are politically stable, although they have high debt levels and unemployment. However, problems of low education standards and high wages in the public sector – which deter unemployed workers from taking lower–paid jobs in the private sector – could prevent an industrial boom, alongside poor infrastructure and governments which are struggling to adapt to the changing political environment. (*Financial Times*, 26 July 2017)

▸▸ New research from Alan Krueger of Princeton University shows that the increasing use of opioids in the USA is impeding its jobs market recovery, as high rates of painkiller usage is linked to falling numbers of men participating in the labour market. It may account for 20% of men's declining labour–force participation from 1999 to 2015, and labour–market participation fell most sharply in areas with higher rates of opioid prescriptions, whilst these prescriptions increased by 356% in the same period. Separate research has shown that nearly 50% of working–age men who are not in employment, nor actively seeking employment, take pain medication each day, and 67% of those men – 2 million people – take prescription pain drugs daily. This phenomenon sheds light on a key problem within the US labour market – even though unemployment is 4%, labour market participation has not rebounded, and is stuck at 62.9% – on a par with the 2014 rate, and lower than the 67% rate last seen in the late 1990s. The rate amongst prime–age men is particularly low – indeed, out of all OECD countries, only Italy has a lower rate. Mr Krueger argues that the use of opioid prescriptions must be addressed to increase particular of these men, highlighting that it affects labour participation by denting motivation and affecting individuals' ability to pass drugs tests. (*Financial Times*, 7 September 2017)

▸▸ Relatively little attention has been paid to private sector investment in global health R&D, with most measurements focusing on public sector expenditure. However, a study published by the Brookings Institute aimed to redress this by quantifying the return–seeking R&D investments in drugs, vaccines and therapeutics by the private sector, which includes pharmaceutical companies, venture capitalists and impact investments. The authors concentrated on overall R&D that focused on these areas, plus global health R&D that emphasizes medical treatments in the developing world, and neglected disease R&D, which focuses on drugs, vaccines and therapeutics for 35 specific illnesses which mainly affect low–income countries. Overall, they sound that at least US$ 159.9 billion is spent on health R&D annually, and that

private sector investment accounts for US$ 5.9 billion of global health R&D in developing countries, mainly from pharmaceutical companies and venture capitalists. Private sector R&D on neglected diseases garners a mere US$ 511 million, mainly from private investors. Much of the growth in private global health R&D is from non–western companies, and looking ahead, the private sector will need to increase to counteract reductions in public health expenditure. The authors also make several recommendations for improving private investment, including creating viable markets, strengthening health governance and tax incentives. They also call for the funding gap between HIV, tuberculosis and malaria, which are relatively well–funded, despite having lower mortality rates than some non–communicable diseases, which affect more people but have less funding. (*Brooking Institute*, 12 September 2017)

▶▶ China is one of the world's largest providers of overseas aid, spending an estimated US$ 5 billion on aid. However, it has a reputation as a rogue donor – funding shoddy projects, mistreating workers coupled with low environmental standards. The benefits of China's aid programme are largely kept secret, but a recent study by AidData looked at 4400 projects funded by China from 2000 to 2014. Their total value was US$ 350 billion, compared to the USA's aid of US$ 424 billion. Unlike the USA, 20% of China's aid is in grant form (US$75 billion – equivalent to the UK), with the rest being concessional lending at below–market interest rates, mainly to Chinese companies working overseas. Concessional lending fell out of favour in the 1990s as it overburdened recipients with debt. Despite this, AidData's study, based on official announcements from Chinese commercial offices and from the finance and planning ministries of recipient countries, indicates that a 100% increase in China's grant aid is associated with a 0.4% increase in recipient GDP after two years. This is in contrast to China's concessional lending, which has no effect on the recipient's GDP, and appears to consist of a subsidy to Chinese companies, alongside bribes to local elites. More positively, AidData's study suggests that aid from China does not harm efforts from other donors. Overall, the study suggests that Chinese aid should focus more on grants, rather than loans. Second, Western agencies should co–operate more with China, to avoid duplication. And lastly, China should be more open about the successes of its overseas aid programme. (*Economist*, 12 October 2017).

▶▶ Richard Thaler won the 2017 Nobel Prize in Economics, and his work on "nudge theory" – credited with helping people save more for retirement, eat more healthily and even with improving men's aim into urinals – is based on the idea that small changes in people's "choice architecture" can steer them towards beneficial decisions. However, nudge theory can also be used to steer people towards choices that work against them. Eg, Uber has developed techniques that push its drivers to work for longer – even at hours and locations that are less profitable for them – with drivers being shown their next fare before they've even dropped off their current passenger. In the UK, bookmakers advertise complex bets to gamblers (eg, whether a certain player will score first), which earns higher profit margins as gamblers consistently overestimate the probability of complex bets. These techniques have been termed "dark nudges", and are becoming increasingly common in highly–complex and often poor value–for–money products, eg, sub–prime mortgages or complex mobile phone contracts. These approaches utilise nudge theory in ways that it was not intended, and consumers may respond by tuning out all nudges, including those which may be beneficial. Mr Thaler himself urges consumers to be vigilant, read the fine print, and give their business to companies that nudge for good, not bad. (*MarketWatch*, 20 October 2017)

▶ Energy

▶▶ The Irish government is discussing projects with Brussels to improve its energy security post–Brexit. All of Ireland's imported gas and electricity flow via the UK, and Ireland is seeking to reduce its reliance on the UK following the UK's departure from the EU. The talks with Brussels are covering potential projects such as a 1 billion Euro (US$ 1.65 billion) French electricity link, and a 500 million Euro (US$ 582 million) liquified natural gas terminal, for which Ireland is seeking EU financial support. The EU has already awarded 4 million Euros (US$ 4.66 million) for preparatory work on the proposed "Celtic Interconnector", which will carry 700 MW of electricity between northwest France and southern Ireland. The EU may also support a liquid natural gas terminal on Ireland's west coast, which could be an attractive entry point to northern Europe for booming US gas exports. Peter O'Shea, from ESB, Ireland's power group, said that both the UK and Ireland have a mutual interest in ensuring smooth and low–cost energy flows between the UK and EU. "Ireland, north and south, Great Britain and Europe are all net importers

of energy and have critical dependencies on each other. I would hope that pragmatism will prevail," he said. (*Power Engineering International*, 27 July 2017)

▸▸ Until recently, economists believed that power generated from offshore wind was an expensive and inefficient way of reducing carbon emissions, but in September 2017 this was blown apart by a massive fall in the cost of offshore wind in an UK government auction. This has led to suggestions that over the next 50 North Sea wind could be as important to the UK, as North Sea oil and gas were in the previous 50 years. Although wind power only accounts for 5% of Britain's energy production, the auction showed how a commitment to wind power can lower its costs to the point where it can compete with gas and nuclear energy. Technological improvements in the industry have also improved its efficiency, and the British supply–chain is catching up by producing more wind turbines. The reformed auction system also promotes competition by allowing companies to decide where they should locate their offshore wind farms, rather than governments. All this bolsters the UK's position as the world leader in off–shore energy, with capacity expected to double by 2020, and investment is tipped to reach US$ 11.5 billion in 2017–21 – more than expenditure on broadband infrastructure. However, pressure on suppliers to cut costs risks sloppy workmanship and delays. (*Economist*, 14 September 2017)

▸▸ The goal of the entire world's population having access to modern, reliable affordable energy by 2030 will not be achieved without full funding, according to Sustainable Energy for All (SEforALL), a body set up by the UN. SEforALL believes that this slow progress undermines effort to end poverty, food shortages and curb climate change, and denies people "a fundamental building block" of prosperity, and that the lack of funding to end the use of polluting fuels for cooking is "shocking". Eg, nearly 90% of Bangladeshi people lack access to clean cooking facilities. Across the 20 countries with the biggest gaps in access, overall investment in domestic clean cooking energy resources averaged US$ 32 million a year, against the estimated annual need of US$ 4.4 billion. Rachel Kyte, the CEO of SEforALL, says that not enough governments – particularly in sub–Saharan Africa – prioritise clean cooking, and there is too much focus on designing more efficient stoves at the expense of providing clean fuels, such as gas and solar induction. However, there are notable exceptions, eg, Kenya, where the increasing use of mobile payments has attracted private–sector investment in "pay–as–you–go" solar energy systems. (*Thomson Reuters*, 18 September 2017)

▸▸ Michael Bloomberg, a UN special envoy on climate change, has extended his US$ 164 million campaign against coal–burning from the USA to Europe, with US$ 50 million allocated to Europe. He has further plans to expand his campaign to the rest of the world. The funding will be used to support grassroots campaigns, research on the health impacts of coal, and legal action against coal plants that are breaking pollution laws. Mr Bloomberg is a prominent opponent to US President Trump's stance on climate change. Coal accounts for 20% of the EU's carbon emissions – Germany and Poland are the main emitters – and Mr Bloomberg aims to accelerate the decline in coal by capitalising on falling prices for renewal energy and rising concerns over air pollution. He credits the mass closure of US coal–fired power stations to civil society advocacy combined with falling costs of renewable energy. He is now looking for partners to extend his campaign into Asia, which burns coal on a large scale. However, he rejects arguments that coal plants are a fast and cost–effective way to bring electricity to the millions of people world–wide who lack access to electricity. "Number one, it is not the cheapest or quickest, and number two, how many people are you going to kill [with air pollution]"? he said. (*The Guardian*, 9 November 2017)

▸▸ On 16 October, China's main planning agency issued a notice to local authorities and state petroleum producers in northern cities, warning that gas supplies will be "insufficient" during the peak demand periods of the heating season – mid–November to mid–March. 2017 saw strong economic growth in China, accelerating gas consumption, and a cold winter will worsen shortages. State petroleum companies were directed to increase gas production and work on pipelines, as well as accelerate gas storage projects and import infrastructure. Gas is a cleaner fuel than coal, and switching from coal to gas for domestic heating will improve China's air quality, but shortages may hamper the government's efforts. The government has raising distribution prices to commercial users to prioritise domestic users, and China's imports of liquid natural gas in September were the second–highest on record. The government has ordered an end to all coal–fired heating in northern cities, leading to a crash programme to scrap coal–fired boilers and build new distribution networks for natural gas. Despite these efforts, air pollution worsened over the Beijing–Tianjin–Hebei region, as concentrations of fine–smog forming particles rose by 10% from the previous year, according to the Ministry of Environmental Protection. (*Radio Free Asia*, 13 November 2017)

▶ Environment

▶▶ China's ban on importing garbage from overseas will take effect at the end of 2017, covering materials such as waste plastic and paper, as well as slag from steelmaking, and waste wool, ash, cotton and yarn. China is a major importer of waste – in 2016, it imported 7.3 million tonnes of waste plastics, valued at US$ 3.7 billion. In its notification to the World Trade Organization of the forthcoming ban, China cited the large amount of dirty or hazardous wastes that were mixed into the solid waste, and were causing serious problems with environmental pollution. China's rapid industrial development has led to it struggling with waste disposal, leading to toxic waterways and cities blanketed in smog. It plans to conduct a nation–wide survey of pollution sources, and has urged local authorities to move quickly by launching local investigations. (*Reuters*, 18 July 2017)

▶▶ Cobalt is a critical part of the lithium–ion batteries used in electric cars, and these batteries account for 42% of the global consumption of cobalt. This will increase further – some analysts predict a 30–fold increase by 2030 – as the world moves away from diesel and petrol cars towards electric cars. 60% of the world's cobalt supplies is mined in the Democratic Republic of Congo (DRC). However, thus far, the average Congolese citizen – who are amongst the poorest people on Earth – has gained little from their country's abundant supply of the metal. Indeed, according to a recent report from Global Witness, 30% the revenues paid to state bodies by mining companies – US$ 750 million – have disappeared. The west has poured in billions of US$ to the DRC in peace–keeping and aid, but foreign mining companies have extracted much more in gold, diamonds, tin, coltan, copper and cobalt. It is incredibly complex to ascertain if cobalt entering the supply chain was sourced without labour exploitation, violence and toxic pollution – and suppliers who boycott Congolese cobalt often ultimately harm small–scale artisan miners – but the same ingenuity which invented the electric car should be capable of solving the dilemma of powering them ethically. (*Financial Times*, 26 July 2017)

▶▶ South Asia is home to 20% of the world's population, and could see humid heat levels increase to unsurvivable levels by the end of the century unless action is taken. According to a study published in *Science Advances*, the region could experience summer heat waves with levels of heat and humidity beyond what humans can survive without protection. The study is the first to look at "wet–bulb temperature", which combines temperate, humidity and the body's ability to cool down, and the survivability threshold is considered to be 35°C. The study examined two scenarios, the "business–as–usual" scenario, where little is done to combat climate change, and the second scenario in which temperate change is kept to under 2°C, as pledged by the 2015 Paris accord. Under the "business–as–usual" scenario, wet–bulb temperatures are expected to approach the survivability threshold over most of South Asia, and exceed it in a few areas by 2100, affecting 30% of the region's population. Farm workers would be worst affected as they have fewer opportunities to escape into air–conditioned environments. However, if global warming can be limited to 2°C, the population exposed to dangerous wet–bulb temperatures would increase from 0% to 2% – less than the 30% under the first scenario – and although temperatures would still reach 31°C, this is still below the fatal thresholder. Lead author Elfatih Eltahirhe, professor of environmental engineering at the Massachusetts Institute of Technology, calls for mitigation of the effects of climate change. "With mitigation, we hope we will be able to avoid these severe projections. This is not something that is unavoidable," he said. (*Jakarta Post*, 3 August 2017)

▶▶ According to a study published in the *Lancet*, global pollution contributes to an estimated 9 million deaths each year – around 1–in–6 of all deaths, whether through dirty air, tainted water, toxic industry etc. If correct, this means that pollution kills three times more people than HIV/AIDS, malaria and TB combined – and most of these deaths occur in developing countries. It found that poor air quality was the main driver, causing heart disease, strokes, lung cancer and other respiratory problems. The largest number of deaths were found in India and China, with an estimated 2.5 million and 1.8 million deaths respectively, and overall the authors estimated that pollution–related health problems and deaths cost 1.3% of developing countries' GDP, compared to 0.5% in developed countries. According to Gina McCarthy, a former administrator at the US's Environmental Protection Agency, addressing this problem is vital to moving people out of poverty, but that climate change would serve to worsen it. Philip Landigan, one of the study authors, states that poor developing countries can and should do more to reduce pollution, and would reap economic benefits from doing so. He also called for developed coun-

tries and aid foundations to support developing countries in reducing pollution. (*Washington Post*, 19 October 2017)

▶▶ A new study used satellite data to track global artificially–lit surfaces, and found that these surfaces are increasing and growing brighter, producing more light pollution at night. In the second half of the 20th century, outdoor lighting grew by 3%–6% each year, due to electric lights. Whilst this has benefitted human productivity and safety, it means that nights are no longer dark enough, with 50% of Europe and 25% of North America experiencing modified light–dark cycles. Light pollution can have serious consequences for organisms, which have evolved in accordance with natural day–night cycles – additional, artificial, light is a stressor, and many organisms have not had enough time to adapt. 30% of vertebrates and more than 60% of invertebrates are nocturnal, and could affect interactions between species. Humans are also affected by artificial light, because certain physiological processes happen in the daytime, and others at night–time, and they often work against each other (eg, shift–workers who work against their biological day–night clocks can experience a range of health problems). The introduction of cheaper LED lighting has led to more energy devoted to lighting, as costs have fallen, and the blue light in LEDS is particularly disruptive for nocturnal patterns. Solutions to the growing problem of light pollution includes using LEDs without a blue component, and positioning light sources so they are not as bright but still effective (eg, dim, closely–spaced lights are more effective than bright lights spread out). (*Seattle Times*, 22 November 2017)

▶ Food, Water and Sanitation

▶▶ The Toilet Board Coalition and Pune Municipal Corporation, India, have announced a collaboration aimed at making Pune the world's first smart sanitation city. The Toilet Board Coalition, a business–led public–private partnership, and the city's governing body, confirmed that they will develop smart, sustainable and resilient sanitation systems, delivered via the marketplace. The project will launch in January 2018, and its three work streams consists of: community toilets, focusing on optimising their usage and behavioural change; waste management and resource recovery; and exploring the use of sensors in the sanitation system for data capture. This is part of Prime Minister Modi's Smart Cities campaign, and Pune has already been selected as one of Mr Modi's "Smart Cities, and has also declared itself an official open–defecation–free city (the Indian government aims to eradicate open defecation by 2019). "Sanitation solutions that improve lives and make our citizens proud is at the centre of our project – working with global and local businesses and leveraging smart technologies," said Prerna Deshbhratar of the Pune Municipal Corporation. (*Cities Today*, 30 August 2017)

▶▶ The majority of New York school students are poor, with 75% qualifying for free or reduced price lunches. However, many children skip lunch rather than admitting that their families cannot afford to pay for it, and the national practice of "lunch shaming" – holding children accountable for unpaid lunch bills – has attracted attention. In light of this, New York City will make all school lunches free of charge, joining cities such as Boston, Chicago, Detroit and Dallas. The city's administration does not expect to spend more on lunches as a result, as the city qualifies for a federal programme that pays for universal free lunches. New York City schools had already provided breakfast, and the city's stand–alone middle–schools have had a free lunch scheme in place that provides lunch to an additional 10 000 children who would not necessarily have qualified for free school meals. (*New York Times*, 6 September 2017)

▶▶ According to the Food and Agriculture Organization (FAO), for the first time in several years, the estimated number of undernourished people has increased, rather than decreased, to reach 800 million people worldwide. This means that the world has much more to do to reach the SDG of ending world hunger by 2030. Food insecurity is also high, and there is little evidence of improvement over the past decade. In the poorest countries, agricultural productivity is very low, with little improvement – and yields are generally lower for smallholder farmers where hunger is concentrated. The situation is worsened by a lack of private credit amongst smallholders, which hampers investment. Current agricultural policy is doing little to alleviate undernourishment, with increasing numbers of non–tariff barriers on agricultural trade, and agricultural subsidies indicate that money is being spent inefficiently (although developed countries have pledged to eliminate subsidies on agricultural exports). Moreover, China, which is becom-

ing a major player in world food markets, is increasing its agricultural subsidies to match the entire OECD. In many countries, total spending on food and nutrition is US$ 10 per person/y, which is insufficient to reduce hunger, and food prices, which are starting to fall, may cause donors to shift attention elsewhere. Significant improvements in data, policies, resources and institutional performance are all required to end hunger by 2030. (*Brookings*, 23 October 2017)

▶▶ Mr Aliko Dangote, Africa's richest man with a net worth of US$ 13.7 billion, has pledged to invest US$ 100 million via his Dangote Foundation to tackle malnutrition in Nigeria's worst–affected areas. It aims to reduce the prevalence of under–nutrition by 60% in these areas, specifically the northeast and north-west of the country. Mr Dangote set up the Dangote Foundation in 1993, which invests in health, education, economic empowerment and disaster relief. The announcement was made at the Global Nutrition Summit, which aims to accelerate the global response to malnutrition. "Nigeria's high malnutrition rate is undermining progress towards improving child health and putting the brakes on economic development. By investing in nutrition, we aim to directly improve the lives of Nigerian families and to empower our citizens to reach their full potential," said Ms Zouera Youssoufou, the Managing Director and CEO and Dangote Foundation. (*Forbes*, 6 November 2017)

▶▶ Cambodia is lauded as one of the most successful countries in getting people to install and use toilets – and key to that success is a peer–pressure strategy developed in Bangladesh and adopted across the world. Pressure from the community inhibits people from defecating in the open, and they are encouraged to use the toilets of friends or family instead, if they lack one of their own. Mr Phuy Seakphy has developed a thriving toilet installation business – the toilets consist of simple concrete pipes sunk into the ground, and he now sells 15–20 toilets a month. Women and girls risk attack if they go into fields at night to relieve themselves. The shortage of toilets in rural Cambodia also has a significant effect on children, with an estimated 33% of children aged under 5 years suffering from stunted growth. "When children are exposed to faeces in their environment, they repeatedly get bouts of diarrhoea. So the good things that are going in are coming straight out," says James Wicken, the country director of WaterAid Cambodia. (*Al Jazeera*, 20 November 2017)

▶ Peace and Human Rights

▶▶ Iran has one of the highest rates of capital punishment in the world – executing at least 567 people in 2016 and nearly 1000 in 2015 – but its lawmakers have proposed changes to Iranian anti–drugs legislation which may abolish the death penalty for certain drug–related crimes, mainly petty, non–violent crimes. The government has faces pressure to reform these laws, as critics highlight that they have done little to deter drug–related crime in a country that is a major transition route for drugs smuggled from Afghanistan. Currently, 70% of all Iranian executions are for drug–related crimes, and can be applied for the trafficking or possession of 30g of heroin or cocaine. In November 2015, Hassan Nowruzi, Iran's parliamentary judicial spokesman, called for reform, revealing that 5000 people were on death row for drugs–related offences – the majority being first–time offenders aged 20–30 years. There are an estimated 2000 Afghan people in Iran's prisons on drug–smuggling charges, and there are concerns that many do not receive fair trials and lack access to defence lawyers. The campaigning group Human Rights Watch has called for a moratorium on the Iranian death penalty whilst the reforms are debated – "it makes no sense for Iran's judiciary to executive people now under a drug law that will likely bar such executions," said Sarah Leah Whitson, the group's Middle East Director. However, the proposed changes are opposed by hardliners in the country's judiciary, who defend their "tough stance" on the issue. "In some cases, including drug trafficking, we're forced to act quickly, openly and decisively" said Ayatollah Sadegh Larijani, Iran's judiciary head. (*Radio Free Europe*, 23 July 2017)

▶▶ In the month following the disappearance of Mr Santiago Maldonado, an activist for the rights of indigenous peoples, thousands of Argentinians have demonstrated across the country, demanding answers to his disappearance. Mr Maldonado was last seen when border police evicted a group of indigenous Mapuche people from lands in Patagonia owned by the clothing company Benetton. Mr Maldonado's disappearance is a reminder of the estimated 30 000 people who died or disappeared during Argentina's 1976–1983 military dictatorship. According to witnesses, Mr Maldonado was taken alive, and government investigations have not uncovered any information on his whereabouts. The UN, Amnesty International

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and Human Rights Watch have said that Mr Maldonado's disappearance requires urgent action from the Argentine President, Mauricio Macri. (*Al Jazeera*, 2 September 2017)

▶▶ Cambodia's Prime Minister Hun Sen's governing party (the Cambodian People's Party, or CPP) has faced widespread condemnation over its actions ahead of general elections scheduled for July 2018. These have ranged from targeting the opposition Cambodia National Rescue Party (CNRP), as well as orchestrating the closure of independent media outlets and restricting NGOs. On 16 November, Cambodia's Supreme Court unanimously ruled that the CNRP be dissolved for its part in plotting a "coup" against the government, essentially eliminating any opposition to the government. The CNRP leader, Kem Sokha, is under arrest for allegedly collaborating with the US to overthrow the ruling CPP – charges which the US embassy has rejected. In response, international donors (including the EU and Sweden) are withdrawing aid from the country, or are threatening to do so, if restrictions are not lifted. Critics argue the government's actions threaten Cambodia's fragile democracy and call the legitimacy of the 2018 election into question. However, Prime Minister Hun Sen remains firm, saying that he would "welcome" any withdrawal of aid, and that Cambodia will rely on assistance from China, one of its few allies. (*Radio Free Asia*, 21 November 2017)

▶▶ The 2017 Ibrahim Index of African Development shows that the rate of progress on human development has slowed over the past 5 years, with progress in education nearly "grinding to a halt", and the public is losing faith in governments' ability across the continent to improve health services. The index measures human development, based on 26 indicators focusing on welfare, education and health, ranking countries and reporting on their progress. Lower commodity prices could have led to budget cuts that may have affected progress, but there is also a risk from complacency following Africa's gains over the past 10 years. Another factor may be the transition from the Millennium Development Goals, which prioritised education and health, to the Sustainable Development Goals, whose wider and more complex objectives may be more difficult to implement. The faltering progress in education is particularly concerning in a region where 41% of the population is aged under 15. Côte D'Ivoire, Egypt and Togo have led Africa in human development progress, with Côte D'Ivoire moving into a period of stability after the end of conflict, and Egypt also stabilising after the Arab Spring in 2014 and improving its provision of basic health services (although its human rights and citizen participation indices have declined). Togo has improved access to antiretroviral treatment, although there are street protests about the transfer of power from the former president to his son. Libya, Ghana and Sierra Leone experienced the greatest deteriorations in the human development index; Libya due to shortages of social safety nets, the Ghanaian public is losing confidence in their government's ability to handle basic health services, and Sierra Leone's efforts to narrow income gaps are losing momentum. Overall, Mauritius, Seychelles and Botswana are leading the continent's development index, whilst Somalia, South Sudan and the Central African Republic languish at the bottom. However, more hopefully, the index found that antiretroviral treatment is the most improved indicator. In 2000, less than 1% of people in need of treatment received it, but in 2016, 54% received it. (*Devex*, 20 November 2017)

▶▶ Yemen has long since lost its title of *Arabia Felix* ("Fortunate Arabia"), suffering from civil wars, tribalism, jihadist violence and appalling poverty – but the ongoing war between a Saudi–led coalition and the Houthis, a Shia militia backed by Iran is the worst yet. It is on the brink of famine, crises over waste disposal, sewerage system and water supplies have led to the worst cholera outbreak in recent history – and the UN estimates that 75% of its 28 million people need humanitarian aid. So far, the outside world has paid little attention, perhaps because it is inured after years of bloodshed in the Middle East – or, more cynically, because Yemen is further from Syria than Europe so Yemenis do not generally seek asylum there. Even setting aside humanitarian considerations, the world cannot afford another failed state that becomes a breeding–ground for terrorism. The war has its roots in the 2011 Arab Spring, when mass unrest forced the president, Mr Ali Abdullah Saleh to step down, but his successor, and the resulting constitutional changes, were rejected by the Houthi rebels, who allied themselves with the former president. The war has dragged on – the Houthis are too weak to rule over Yemen but as a well–entrenched militia, too powerful for Saudi Arabia to defeat. UN–led peace talks have led with the demand that the Houthis surrender, which is unrealistic. A more pragmatic approach would be to freeze the conflict, and find another mediator, such as Oman or Kuwait. A deal should involve the phased withdrawal of Houthi fighters from key areas, and the end to the Saudi blockade. Yemen needs an inclusive government, elections, and a new state structure, and Saudi Arabia will need guarantees that Iranian arms are not flowing into Yemen. (*Economist*, 30 November 2017)

▶ Science and Technology

▶▶ Researchers from New York University are beginning to recruit participants into "The Human Project", which will enroll 10 000 people to share a trove of personal information, including cellphone locations, credit card swipes, blood samples and life–changing events – over the next 20 years. The project will channel the data streams to build a picture of health, ageing, education and other aspects of human life. Although the "Human Project" is one of many "big data" health studies, its approach on the scope of data it plans to simultaneously collect is unique. Participants will be invited to join, following demographical-ly–representative groupings, and will be screened for blood groups, genetics and IQ, and will give access to medical, financial and educational records, plus cellphone data. They will be given activity trackers, weighing scales and surveys, and will have follow–up tests at 3 years. The project team hope that the re-sults will illuminate the linkages between health, behaviour and circumstances, and will shed light on conditions from asthma to Alzheimer disease. The data will be subject to stringent protection measures, with researchers safeguarding data from all eventualities apart from major terrorism probes. (*STAT news*, 19 June 2017)

▶▶ The World Health Organization estimates that there are 2–5 million people with missing limbs in the developing world, many of whom do not have prosthetic limbs. To help overcome this, Ashraf Mizo, a Sudanese engineering student, is working on simplified and inexpensive prosthetic limbs through 3–D printing technology and machine learning. Until recently, 3–D printing has been viewed as far too expen-sive for prosthetic limbs, and that prosthetic limbs are regardless too complex for 3–D printing. Howev-er, Mr Mizo uses a simplified calibration system and a reduced number of actions –open, close, pinch and grip – that enabled him to print a prosthetic arm for US$ 20. Although the prototype has not yet been tested on amputees, Mr Mizo plans to partner with an amputee organisation in Sudan to start fitting pros-thetic hands onto patients. (*Forbes*, 31 August 2017)

▶▶ In the USA, radiologists on average earn US$ 400 000 a year – nearly double the salary of a family doctor – but many radiologists are concerned over job security. MRI and CT scans are now routine pro-cedures, and their data can be stored digitally, so radiologists have to assess many more images – a radi-ologist may review 20–100 scans a day, and each scan can have thousands of images. This makes radiol-ogy particularly amenable to artificial intelligence and machine learning, as it is based on humans examining pictures and discerning patterns amongst the images – which computers can excel at. Tech-nological companies, such as IBM, Google and GE are developing technologies that uses machine learn-ing – training a computer by feeding it thousands of images – that may lead to an algorithm that can di-agnose heart disease or strokes more quickly and cheaply than a human. These algorithms could also potentially check a single scan for multiple diseases. However, Dr John Mongan of UCSF is unconcerned about radiologists being replaced by artificial intelligence in the longer–term; he believes that their role will evolve to spend less time examining images and more time selecting algorithms and interpreting re-sults. If radiologists can work with artificial intelligence, they may benefit from it, rather than be replaced by it. (*NPR*, 4 September 2017)

▶▶ The 2017 Nobel Prize in Physiology and Medicine was awarded to Jeffrey C Hall, Michael Rosbash and Michael W Young for their work on the molecular mechanisms that control the body's circadian rhythms. They used a gene isolated from fruit flies to determine how it encoded for a protein that accu-mulated in cells at night, and then degraded during the day. Their research casts light on the biology of humans and other multicellular organisms whose biological clocks function on the same principle of 24–hour rhythms of sleep and wakefulness, plus functions such as blood pressure, heart rate, alertness, tem-perature and reaction times. The Nobel committee judged that their work was pivotal, because under-standing that misalignment between a person's lifestyle and the rhythm dictated by an inner time–keeper could affect well–being and could contribute to the risks for various diseases. (*New York Times*, 2 Novem-ber 2017)

▶▶ South Africa has the highest incidence of HIV in the world, but of the 7 million people infected with HIV, only 50% are receiving treatment, and the country's public health system is being pushed to break-ing–point. It is hoped to bring HIV under control by doubling the number of people receiving treatment, but the health system cannot afford to double the number of doctors, nurses and pharmacists. To cope

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with demand, the health system is making more use of technology, including robots. Eg, the Helen Joseph hospital, South Africa's busiest HIV clinic, uses a robot pharmacist to collect and package drugs; and although its work is checked by humans, overall waiting times at the clinic have fallen from 4 hours to under 20 minutes. Researchers are now working on ATM–style medication dispensaries which will be even swifter. Moreover, Africa as a whole makes up 66% of the world's pregnancy and childbirth–related deaths, despite having one–sixth of the world's population – and 1–in–9 children dies before their 5th birthday. Many of these deaths could be avoided by simple diagnostic tools, and new technologies are improving this. For instance, the electronics company Phillips have developed a wind–up ultrasound machine that requires no electricity supply and provides a digital printout of a foetus's heartbeat, that more accurately identifies urgent cases than the trumpet horn which is normally used. Phillips have also developed an easily–transportable solar–powered chest monitor that measures a baby's rate of breathing to help diagnose pneumonia. Companies such as IBM are using artificial intelligence to determine how drug–resistant TB spreads, and how genes that protect against malaria contribute to an increased risk of certain cancers. Mobile phone apps are being used to train health workers, and Médecins Sans Frontières is experimenting with a smartphone to determine if a cough indicates asthma or pneumonia. According to Solomon Assefa, the head of IBM's research in Africa, the continent's shortage of health professionals is forcing it to experiment with technology. High–income countries are not yet under the same pressure, but ageing populations and the increasing burden of chronic diseases may lead them to learn from Africa's experiences with technology. (*Economist*, 9 November 2017)

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Pharmaceutical industry, non-communicable diseases and partnerships: More questions than answers

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> Partnerships with pharmaceutical companies have shown some success for example with HIV/AIDS, vaccines and neglected tropical diseases.

When 21 biopharmaceutical companies recently launched the Access Accelerated Initiative (AAI) on prevention and care for non-communicable diseases (NCD) [1] in Davos, Switzerland, it was described as a 'global, multi-stakeholder collaboration'. The need for partnership is included in the Sustainable Development Goals (SDG). SDG 17 aims to "Revitalize the global partnership for sustainable development" and requires inclusive partnerships between governments, civil society and the private sector [2].

The launch of the AAI leaves many questions unanswered regarding exactly how this partnership model is organized. From the little information publicly available, AAI presents a skewed view of what partnerships in global health should be. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acts as its Secretariat and no government or multi-lateral agency, besides the World Bank, is included. The Union for International Cancer Control (UICC) represents civil society. The AAI states that other NCD organizations will be involved, but these organizations are dwarfed by pharmaceutical company partners and most, including the UICC, are reliant on funding from these same companies [3].

Partnerships with pharmaceutical companies have shown some success, as seen with HIV/AIDS, vaccines and Neglected Tropical Diseases (NTD) [4-7]. In these partnerships each stakeholder had a specific role. Funding came from bi-lateral and multi-lateral donors, civil society played the role of advocate and implementer, and the pharma-

> Responsibilities in addressing access to NCD medicines lie with the World Health Organization, governments, donors, and civil society with the role of the private sector to complement these roles; not to replace them.

> Any partnership with the private sector needs to be framed within strict rules of engagement to avoid any perceived or real conflict of interest.

ceutical industry either developed new products or made existing medicines available for free or at differential prices with long-term pledges.

Responsibilities in addressing access to NCD medicines lie with the World Health Organization (WHO), governments, donors, and civil society. The role of the private sector is to complement these roles; not to replace them. Transparency in company initiatives is often lacking. It is therefore welcome news that AAI will be evaluated by the Boston University School of Public Health. However, this model of partnership raises the following questions:

1. What is the exact agenda in terms of diseases, approaches and countries, with stated objectives, baseline data and targets? How has this agenda been set and who has been involved?

2. Have the intended beneficiaries (patients, governments) been consulted and are locally available structures (such as national treatment guidelines) respected and supported? In general, are the WHO Guidelines for Drug Donations followed? Which partners are responsible for the various components of the program?

3. How will the AAI interact with a variety of other stakeholders, nationally and globally?

4. How will long-term sustainability be achieved?

5. How will accountability to the beneficiaries (patients, governments) be ensured?

NCDs are an unprecedented challenge globally. Universal access to NCD medicines requires long-term investment by all stakeholders, including companies. Long-term sustainability through locally available structures and resources should be a guiding principle in all phases of such initiatives. The SDGs and WHO's Framework of Engagement with Non-State Actors, see an active role for private sector engagement. However, any partnership with the private sector needs to be framed within strict rules of engagement to avoid any perceived or real conflict of interest [8], and need to publicly address the fundamental questions we propose.

Photo: from David Beran's own collection
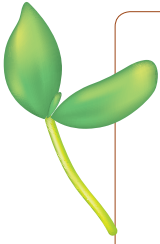
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Why ethnography matters in global health: The case of the traditional birth attendant

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> Ethnography produces robust and reliable knowledge that makes essential contributions to multi-disciplinary and inter-sectoral efforts to solve pressing global health problems.

The representative from the foreign aid agency, a woman with whom I had crossed paths several times in the small town of Mangochi in southern Malawi, banged her fist on the table. "How can we get them to distribute condoms? They should be distributing condoms!" She was referring to the traditional birth attendants (TBAs) in the Monkey Bay Safe Motherhood project that we were there in the meeting to discuss. She envisioned them as ideal community actors in the HIV prevention project she worked for. I had been working in Monkey Bay for the past three months evaluating a Safe Motherhood project. I was also a graduate student in anthropology at the time and therefore inclined to take an ethnographic approach to my task. I knew the TBAs wouldn't distribute condoms. I had been to their homes to talk to them about their work and had asked them as politely as it is possible to do so how they felt about distributing condoms. "Oh no," they invariably told me. "We don't do that. It's not our place to talk to men about that." I had also watched as they slid the 'Safe Birth Kits' they had received as part of their training out from under beds or curtained closets, opened the lids to reveal lengths of condoms still in their packages, closed the kits again and slid them carefully back into place. Imagined by a foreign aid agency to be working in the realm of 'reproductive and sexual health', these TBAs refused. Their work was attending births. They did not fail to fit the bill, they refused it.

Many who work as practitioners in global health could recount similar stories. They might include them in project reports to add texture or to illustrate a point, but anthropologists consider such stories ethnographic data that, with proper context and analysis, constitute reliable and robust knowledge. In this article I will argue that ethnography matters in global health as an essential component of interdisciplinary efforts to understand and address complex global health problems.

But first let me continue the ethnographic story. The information I shared in the meeting room in Mangochi – that TBAs were highly unlikely to ever distribute condoms within their communities – may have gone one of three ways. It may have been ignored and the HIV prevention project may have continued to press for community based condom distribution by TBAs. It may have been noted as a 'cultural barrier' to achieving the goals of the project and become the object of a new set of strategies – adding a component on the importance of condom distribution in the next round of TBA training sessions and refresher courses, for example. Or the information I shared may have been taken as new 'evidence' that provoked a rethinking of the means by which to achieve project goals. I will never know. I wrote up my report on the Safe Motherhood project which included the recommendation that TBAs should not be pressed to distribute condoms; it was not a cultural barrier to be overcome by education or training but a faulty assumption about the scope of practice of these specific TBAs in this particular setting. I would venture to say that trying to get TBAs in rural Malawi to distribute condoms did not work for 'cultural reasons' – but only on the understanding that these 'cultural reasons' lay with the foreign aid agency that suggested it

as a strategy in the first place. The idea that cultural barriers to change must be combatted for interventions to succeed is a staple of global development thinking. But global health communities have cultures too: sets of assumptions, taxonomies, and rationales that just as surely contribute to the outcome of local health projects.

WHY ETHNOGRAPHY MATTERS

Ethnography matters for contemporary societies…This claim derives from the very activity of the ethnographer – a presence both involved and detached, inscribed in the instant and over time, allowing precise descriptions and multiple perspectives, thus providing a distinctive understanding of the world that deserves to be shared [1].

Ethnography is the hallmark of the discipline of anthropology. It involves following the everyday lives of people over long periods of time. Anthropologists immerse themselves for months and years in the communities they seek to understand, learning local languages and living to a great extent as local people do. The kinds of communities that anthropologists study are broader now than in the past. A rural village, a busy urban health clinic, or a group of foreign aid workers in their field offices: these are all ethnographic sites for anthropologists. Though lives may be framed by big events and issues, it is the quotidian that is the essence of ethnography. Even life in exceptional times and situations – conflict zones, prisons, refugee camps, epidemics – develops patterns and ways of being. At the same time, ethnographers approach communities and cultures as dynamic entities with the capacity to change – whether the change is initiated from within or without.

The point I want to stress here is that ethnographers seeks to make visible the practical and moral worlds and actions of individuals and cultural groups, but not in isolation of history and politics. Indeed, critical ethnographers excel at illuminating the connections between the micro and macro levels. Ultimately, the goal of ethnography is to offer better accounts of social phenomena than one can from a distance, from secondary accounts, or from rapid appraisals. By this method, ethnographers produce knowledge that is robust and reliable, if not reproducible.

THE CASE OF TRADITIONAL BIRTH ATTENDANTS IN GLOBAL MATERNAL HEALTH

To illustrate how ethnography matters in global health, I will return to the case of the Traditional Birth Attendant deployed in maternal health interventions. This requires a bit of history. The first global initiative to address the problem of maternal mortality was the Safe Motherhood Initiative (SMI), launched in 1987 by the World Health Organisation (WHO), the World Bank, and the United Nations Population Fund (UNFPA). At that time the global maternal mortality rate was estimated at 500 000 a year – vast majority of deaths occurring in the global south.. The stated goal of the initiative was to reduce this number by half by the year 2000, through a package of upgrades to health systems, personnel, and family planning activities. One of the key interventions was the training of birth attendants to better cope with births at the community level and to identify and refer women at risk to health facilities. UNICEF and other organisations had been training TBAs since the 1970s and it appeared a progressive move to acknowledge traditional medical cultures and incorporate local practitioners in a more systematic way.

But a little more than a decade after its launch, the TBA component of the SMI was reviewed, deemed a failure, and side–lined in favour of increasing the number of 'skilled birth attendants' globally [2]. The decision caused controversy at the time, with many practitioners and researchers arguing that the work of TBAs had not been properly understood or evaluated [3]. What if ethnographic data on birth attendance had mattered in this effort from the beginning? Would we have better understood what roles TBAs were already playing and what roles they could be expected to play? On the basis of such knowledge of local logic and practice concerning pregnancy and birth, could interventions have been designed and launched to appropriately train and support TBAs to make a difference?

As early as 1978 anthropologist Brigitte Jordan had described ineffective and inappropriate methods used in the

> The history of global policy on the training and incorporation of traditional birth attendants in campaigns to reduce maternal mortality illustrates the critical importance of ethnographic data in the design and implementation of effective interventions.

Photo: from author's own collection (used with permission).

training of Maya midwives in the Yucatan: didactic rather hands–on learning, lack of cultural sensitivity by trainers towards *parteras,* and no follow–up [4]. In addition to documenting pedagogical problems with training and supervision, some anthropologists began to call into question the very notion of a universal TBA. In Nepal, for example, there was no local equivalent of the TBA. The women who came forward to receive training had no special experience or expertise with childbirth; TBAs had to be "invented" to fit into SMI activities [5]. Similarly, in Tanzania among Sukuma communities, there was no distinct tradition of midwifery and many women gave birth with female relatives or alone. Some 30% of women identified and trained as TBAs by a local SMI project had never attended a birth before [6].

Anthropologists identified other problems as well. Guidelines for identifying women to be trained as TBAs did not consider the reality that factors such as ethnicity, language, religion and kinship can be more important to women and their families than training in the choice of a birth attendant [7]. In Malawi I observed that many nurse–midwives resented being drafted into the role of TBA liaison by SMI policy. Yet in some places in some ways TBAs were working effectively – able to identify women with complications and refer them to health facilities, for example. Ethnographic data could have provided insight into why.

Not only were TBAs deemed failures in the reduction of maternal deaths, they also came to be seen as obstacles to development for their failure to take on these new roles designated for them by SMI policy. Anthropologist Denise Roth Allen sums it up well:

> When women who have had no experience delivering babies are somehow turned into traditional birth attendants in the span of a ten–day training course, it is hardly surprising that TBA training programs have not produced the results policy makers and program planners originally intended; nor is it surprising that pregnant women residing in rural areas perceive some of these TBAs as risks rather than as sources of labor support when birth is imminent [6], p. 115.

The irony is that the SMI had tried to respect and incorporate local tradition rather than steamroll it. But the local imagined by the SMI was paradoxically too general; the TBA was imagined as a universal type. Significantly, she was also imagined as being able to improve maternal health without the aid of a functioning health care system in many places and in the midst of an HIV epidemic in others. Some critics charged that TBAs had been scapegoated.

A recent article in this journal has called for the 'return of the traditional birth attendant' arguing that it makes pragmatic sense given that so many women in low resource settings still do not have access to adequate health services and that "for many women for a range of reasons TBAs are preferable to hospital care" [8]. As maternal mortality remains high on the global health agenda and the search for innovation in research and interventions continues to scale up, ethnography matters more than ever. It adds context and history to the understanding of present day health challenges for people and populations around the world rather than seeing them as locally made and isolated problems of underdevelopment or culture. It can illuminate the logic and rationale of people and communities at the local level and see them in their particularity, not in their global otherness. It can help explain why some interventions fail and others succeed. It can help identify modes of change that make sense not universally but in a given context.

In sum, ethnography matters in global health because it produces distinctive, locally grounded knowledge that can contribute to the multi–disciplinary and inter–sectoral effort to create effective solutions to pressing and persistent global health problems. Why global health culture has not embraced ethnography is a question ripe for discussion. Certainly, the dominance of quantitative research and the trend towards accountability metrics in global health is a factor, even though qualitative methodologies are better able to capture the social relations of health care so fundamental to the changes in knowledge and behaviour most global health interventions seek [9,10]. There are several directions we might take to change

the marginal status of ethnographic knowledge in global health. Anthropologists can continue to conduct critical ethnographic studies of global health policy–making circles to offer insight into these 'epistemic communities' in terms of the knowledge and values they share and the fiscal, ideological and political pressures they must abide. Collaborative research is another way forward, taking on the challenges of cross–disciplinary communication in both the conduct of research and writing [11]. We can also disseminate the results of our research to new audiences. However we move forward, making the case for ethnography is an important part of the work of anthropologists engaged in global health research and practice today.
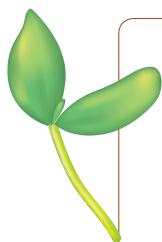
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Chronic pain in refugee torture survivors

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> The number of refugee torture survivors world-wide is accelerating given violent global conflict, and healthcare providers are more likely to encounter refugees in their practices.

The World Health Organization has declared the existing refugee migration an international humanitarian disaster, considering it the worst humanitarian crisis since the Second World War. The United Nations High Commissioner for Refugees in 2015 documented over 65.3 million forcibly displaced people worldwide, including more than 21 million refugees; this number will undoubtedly increase considerably given the acceleration of violent global conflicts and the resulting numbers of displaced people [1]. Despite a universal ban by the United Nations, 50% of all countries, including 79% of G-20 countries, practice systematic torture, affecting an estimated 5%-69% of refugees in the world [2]. Physicians in developed countries will typically encounter survivors of torture as refugees or asylum seekers [3]. Medical anthropologists have highlighted the importance of evaluating non-medical factors such as economic and social determinants of health, during the process of refugee assessment [4]. Experienced physicians in the field recommend taking a multimodal, interdisciplinary approach to refugee treatment, such as the use of alternate therapies including acupuncture and *t'ai chi* [5]. Yet the holistic paradigm of assessment and rehabilitation is incomplete without considering the potential of chronic, debilitating somatic pain experienced by survivors of torture.

Torture leads to a combination of physical and psychological trauma. In a systematic review of the prevalence of psychiatric conditions in refugee populations, Post Traumatic Stress Disorder (PTSD) was found in 30.6% and depression in 30.8% of individuals [6]. The literature on refugee survivors of torture has similarly demonstrated a high prevalence of chronic pain, with some data showing an incidence as high as 83% [7]. To describe this, our group conducted a retrospective, IRB approved study (N = 11) of an immigrant South Asian population in New York City using a novel pain assessment tool. Participants in the study were self-reported survivors of government-sponsored torture in Punjab, India. Torture was employed by police authorities in order to punish individuals, extract confessions, or obtain desired information. Most common mechanisms of physical torture identified included slapping, kicking, and punching, stretching of legs greater than 180 degrees, and muscle crush injuries, each with the persistence of severe chronic pain over two decades after torture. Constant, debilitating pain was described by all subjects, often related to specific mechanisms of torture and with no confounding medical condition to explain the disability (**Table 1**).

Table 1. Mechanism of torture, chronic somatic pain in subjects and whether or not this pain was related to torture mechanism.

Subject number	Chronic pain	Pain distribution related to torture
1	Yes	Yes
2	Yes	Uncertain
3	Yes	Yes
4	Yes	Yes
5	Yes	Yes
6	Yes	Yes
7	Yes	Yes
8	Yes	Uncertain
9	Yes	Yes
10	Yes	Yes
11	Yes	Yes

A number of studies have detailed mechanisms of torture and their specific pain sequalae. For example, falanga, or blunt trauma to the soles of the feet, may result in compensated gait and peripheral neuropathy, hanging from the limbs is associated with brachial plexopathy, and leg suspension or hyperextension is correlated with lumbo-

> In addition to psychological trauma, physical trauma suffered by torture survivors results in chronic somatic pain that is often under or misdiagnosed by physicians. A rapid screening tool for chronic pain, similar to those for MDD and PTSD, should be utilized when evaluating refugee survivors of torture; ultimately guidance from pain specialist physicians may be warranted.

sacral plexus injury [8]. Studies of asylum seekers have found that physical symptoms are approximately twice as frequent as psychological symptoms, and are two to three times as frequent in survivors of torture as compared to non-tortured asylum seekers. Psychiatric syndromes such as PTSD, Major Depressive Disorder, and somatization may contribute to chronic pain. Yet several studies of survivors demonstrate that the physical sequalae of torture actually accentuate or modulate the psychological sequelae, potentially more than the converse. Notably, the presence of chronic pain impedes psychiatric treatment; without diagnosing and treating pain in survivors of torture, both physical and psychiatric rehabilitation are incomplete and inadequate [9].

The United Nations' Istanbul Protocol is the international standard for the medical evaluation of refugees [10]. It recommends a broad assessment of pain incorporated into the physical examination of individuals. Yet, physicians are not adequately performing this pain assessment in their evaluations of refugees [3]. Limitations potentially include the unfamiliarity of general physicians in diagnosing pain syndromes and the absence of a rapid screening tool for use, similar to the screening tools used for PTSD and MDD, which trigger evaluation by a specialist. Often, the complex clinical picture of survivors of torture results in the confounding or eclipsing of somatic pain by mental illnesses. This is noted to be particularly pronounced in developed countries where the clinical and research focus has been on the psychological rather than the physical impact of torture. The missed pain diagnoses impact treatment, as emphasis is placed on psychotherapeutic models that attribute pain to somatization, and primarily focus on psychological and alternate therapies during rehabilitation.

With the overemphasis on the psychological components of refugee health, the implementation of a rapid, chronic pain-screening tool for general providers in refugee clinics should be considered. The use of such a tool may trigger further questioning on pain or referral to a specialist. In this context, pain physicians, who have yet as a specialty to engage with refugee health, have a noteworthy diagnostic and treatment role to play. For example, Complex Regional Pain Syndrome, a devastating medical condition that may result from torture, is not mentioned in the Istanbul Protocol or any of the existing literature to-date on torture and pain, and would likely only be diagnosed and adequately managed by a pain specialist physician.

Future studies should aim to identify and validate an appropriate, rapid screening tool for pain to be used in refugee clinics. Guidance should be sought from experts in the field of refugee health, including general physicians, psychiatrists, medical anthropologists, and social workers, amongst others. Ultimately, pain specialist physicians must become integral to the medical care and rehabilitation of survivors of torture.

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VIEWPOINTS

Biodiversity, drug discovery, and the future of global health: Introducing the biodiversity to biomedicine consortium, a call to action

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Looking to nature for medicine is nothing new – we have been doing it for tens of thousands of years and although modern pharmaceutical science has come a long way from those ancient roots, nature is and will always be an important source of useful compounds and inspiration. Dismissing nature in this regard is a huge mistake as evolution is the greatest problem solver and the myriad compounds produced by the immense variety of species we share the planet with have been honed by three billion years of trial and error. However, with every bit of habitat that disappears under the plough or concrete we impoverish nature and deprive ourselves of potential medicines.

The preservation of biodiversity is perhaps the single most important building block for achieving the 17 Sustainable Development Goals set by the United Nations. For many of these goals, the importance of

> Increasing protection and responsible use of biodiversity will increase global health through discovery of new biomedically relevant compounds.

preserving biodiversity is obvious, e.g.SDG-2 (Zero Hunger), SDG-13 (Climate Action), SDG-14 (Life below Water), and SDG-15 (Life on Land). This argument holds true for the other global goals including, but not limited to, SDG-3 (Good Health and Well-being), SDG-10 (Reducing Inequalities), and SDG-12 (Responsible Consumption and Production). Preserving biodiversity in many landscapes and natural habitats free for people to enjoy and access both locally and worldwide, rather than only in museum collections and zoos is critical for understanding life, the workings of the biosphere and for developing methods to sustain the quality and longevity of human life. Of comparable importance, access to biodiversity as a living, evolving aspect of our planet has the potential to increase the public's appreciation for these systems and processes.

Preserving biodiversity is in our self-interest. Nowhere does this ring truer than in drug discovery. The preservation of biodiversity provides a vital link to critically expand the molecular diversity necessary for successful drug discovery efforts in the future. Drug discovery from wild species has always been, and will continue to be one of the most critical for most if not all aspects of health care, disease prevention, and wellness [1]. In addition, chemical reagents, whether from natural or synthetic sources, are non-renewable, and using these reagents depletes future resources. Resources and knowledge (both traditional and modern scientific) about the ecology, taxonomy and usage of medicinally important organisms are too precious to squander. Consequently, all drug discovery programs, synthetic or natural, need to build the concept of sustainability into their research models.

Biodiversity therefore becomes critical to future drug discovery yet, there is alarming loss of biodiversity. Modern extinction rates are about 100 to 1000 times greater than extinction rates calculated over past eras [2]. Though new species are regularly discovered, known species go extinct at a rate 1000 times higher than the discovery of new species [3]. This ongoing loss of biodiversity is altering ecosystem functions and the ability to provide goods and services for human health and well-being. In the case of drug discovery, according to some estimates, our planet is losing at least one important drug every two years [4]. Further, the irreversible loss of traditional knowledge on the medicinal use of plants and animals and the loss of molecular diversity is concomitant with the extinction of microbes, plants, fungi, and animals. The complementary losses threaten biomedical research, and in turn, the survival of humans.

The sustainable development of natural products will not be possible without taking biodiversity conservation into consideration. While plants are commonly used for medicinal purposes, new possibilities are emerging from organisms that are incredibly diverse biologically and chemically, but relatively understudied, such as arthropods and fungi, particularly in many countries deemed as 'biodiversity hotspots' [5]. We can be certain that we share the planet with an enormous variety of species. A very recent estimate of 1-6 billion species is certainly realistic when we take into account parasites, parasitoids and endosymbionts [6]. Knowing exactly where to look among all of this life, especially the hyper-diverse tax, and obtaining sufficient quantities of starting material have been an issue, historically, but new approaches and technology will surmount these stumbling blocks. Overall, the limitations of combinatorial chemistry and high-throughput screening, together with the promise of phenotype-based screening, transcriptomics and synthetic biology suggest the arrival of a new era of drugs derived from natural extracts [7–10]. We believe that collecting, curating, and disseminating knowledge on biodiversity as it relates to the treatment of human diseases will promote the conservation of bio- and molecular diversity and, simultaneously, create the international cooperation needed to safeguard well-being for all communities.

Sound ethical oversight and responsible policy implementation needs to accompany exploration of medicinal species, whether bacteria, fungi, plants or

Photo: Illustration created by Milica Pešić using CC0 Creative Commons images (no attribution required).

> The Bio2Bio consortium, composed of researchers from across the globe and from many disciplines, aims to develop new tools for protecting biodiversity whilst making new biomedical discoveries and empowering local communities.

animals, for drug discovery. In developing and low-income countries, there is a significant amount of biodiversity that is understudied and available for exploration. These areas are likely to be under disproportionate pressure as medical research turns to biodiverse areas for new drugs. Conversely, developed nations have lost biodiversity while achieving economic progress [11]. Losing novel molecules at the expense of economic progress undermines solutions for human health and economic revenue for the communities where biodiversity should be protected most.

Future efforts to explore biodiversity for drug discovery must consider the interests of indigenous people, respect for their knowledge, and those living in developing, low-income countries. In developing countries, plants are a primary source of health care. When large pharmaceutical companies obtain medicinal plants or purchase lands that support their native habitat in order to make new drugs, these drugs and the plants themselves can become unavailable or unaffordable to the local people who will have no means to buy the products that are developed from these sources. Local plants, which contain mixtures of phytochemicals used as herbal medicines, are far less expensive, and often more available to economically challenged communities than are compounds that are isolated, purified, standardized, and subjected to clinical trials. In addition, local communities may suffer because they may be displaced from culturally important traditional lands. Further, traditional knowledge of species properties and preparations may be lost as medical research forces "western" values and approaches to medicine on diverse local populations.

At both the local and global scales, we should not satisfy our own needs at the expense of future generations, or indeed of other species on Earth. Ensuring the health and safety of other species is in our interests as a healthy planet for humans relies on a rich variety of species. Furthermore, ecosystem governance is also required if significant problems in biomedicine are to be solved through the analysis of global biodiversity.

To safeguard indigenous communities, protect biodiversity, and sustainably pursue drug discovery for the benefit of everyone, it is of paramount importance to strengthen the international implementation of the following practices:

- Investigate and standardise natural products: therapeutic potential, chemistry, ecology, availability and potential to cultivate, traditional use, *in situ* and *ex situ* conservation, sustainable trade, and impacts by climate change, with special focus on indigenous medicinal species with potential therapeutic properties.

- Implement ethical and governance models to engage with diverse indigenous communities to collect existing knowledge on species of interest, and create online databases for easy access, dissemination, and equitable distribution of benefits.

- Promote open inter-disciplinary domestic and international dialogue and information sharing among academics, physicians, patients, policy-makers, commercial bodies, and local and indigenous community stakeholders in the areas of medicine, health and wellbeing, with special focus on understanding different cultural norms and language needed to describe traditional medicine.

- Establish best practices for sustainable natural product collection, production, storage, and preparation–with special attention to safeguard traditional family preparations and assurance that value is returned to local communities, and standardise high capacity bio-molecular and cell-based assays in testing these natural products.

- Raise awareness of the long-term economic benefits of protecting biodiversity over the short-term benefits of habitat destruction and unsustainable resource extraction.

- Promote best practices in sustainable commercialisation of natural products that consider the balance of ecosystems and population needs and the implementation of a fair and equitable share of benefits among current and future stakeholders.

An urgent international and interdisciplinary initiative is required to promote partnerships among diverse stakeholders high, middle, and low-income countries to protect existing knowledge and biodiversity and

to support scientists in evaluating natural product-based therapeutic agents in a standardised and sustainable manner. Formation of multilateral, multidisciplinary research consortia that are global in scope is the pressing need to achieve these goals. Further, public-private partnerships will likely play key roles in addressing this challenge.

New funding models by international and government agencies, pharmaceutical companies, academic institutions, non-governmental organisations, scientific societies, and private foundations/donations are needed to promote work on:

- Collecting, curating, and disseminating information locally, regionally, and globally, from various disciplines regarding historical, current, and potential use of the remaining species for control and prevention and treatment of human diseases in order to promote research, protection, conservation, and international cooperation.

- Connect governmental, research and medical organisations focusing on collecting and testing natural products, developing biological and biomedical assays, health/nutrition regiments, ecological protocols, policy development, and such, to create a common understanding, standard protocols, and best practices in natural treatment and drug development in the interest of the survival of humans and other species.

In order to achieve the above goals, we have established a consortium of early-career scientists representing a wide range of disciplines and countries (**Figure 1**). The Bio2Bio (Biodiversity-to-Biomedicine) consortium will 1) promote exchange of traditional and modern knowledge across disciplines and borders, 2) build a unified framework for sharing resources and data while conforming to international treaties and local regulations, and 3) create an interdisciplinary knowledge hub to communicate research and empower the public, physicians, patients, and policymakers to create a unified approach to selecting, protecting, and undertaking research of the remaining wild species on our planet.

In conclusion, it is crucial that governments, global organizations, and local stakeholders come together to agree on preservation of remaining hotspots of biodiversity through development of partnerships. Activities should include the collation and generation of knowledge about the regions and their species' potentials and provide education and collaborative outreach to local governments, decision makers, and stakeholders.

Figure 1. Schematic representation of the global and interdisciplinary nature of our proposal. Names of the selected research subjects to be included in our consortium are indicated over the globe/map of the world in the shape of 'Tao', with disciplines being distributed according to their relation to each other, in the context of our initiative, to form two large interconnected groups 'Global South' and 'Global North', characteristic by overall tendency to 'biodiversity and traditional knowledge' and 'technology and modern knowledge', respectively. The metaphorical relation to the ancient and modern Chinese symbol of 'Tao' is demonstrating the holistic or 'non-dualistic' approach to the solution to biodiversity and biomedicine problems, requiring acknowledgement and cooperation of bigger scientific community in order to promote mutually beneficial co-existence of humankind with other species.

This largely academic group will also seek to engage individuals and organisations outside of academia via our extended professional networks to help meet the objectives of the consortium. In addition, we invite new members, contributors, and funding opportunities. If you would like to learn more, please contact us at info@bio2bio.net. Together, we can create a new paradigm in protecting biodiversity for sustainable drug discovery that will benefit humanity and the planet.

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The National Evaluation Platform for Maternal, Newborn, and Child Health, and Nutrition: From idea to implementation

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Accelerating progress in women's and children's health requires scaling up efficacious interventions and measuring progress towards defined targets. However, determining what is effective in a particular setting and optimizing investments is challenging given the complexity of health systems and the diversity of contexts surrounding maternal, newborn, and child health and nutrition (MNCH&N) policies and programs in low– and middle–income countries (LMICs). There have been various global efforts to synthesize evidence (eg, World Health Organization Guidelines; various Lancet series on maternal child health and nutrition issues, Cochrane Collaborative reviews, Disease Control Priorities Project and monitor progress towards shared goals (eg, Sustainable Development Goals, World Health Assembly 2025 Nutrition Targets, the Countdown to 2030, Family Planning 2020) which have some influence on country-level priorities and plans [1–6]. Ultimately, however, national and sub-national stakeholders want evidence from their country to guide their policy and program decisions. Too often this evidence is not available when and where decisions makers need it.

Photo: Two task team members in Tanzania. From the private collection of Rebecca Heidkamp.

The National Evaluation Platform (NEP) is a systematic approach to identifying, compiling, and rigorously analyzing data from diverse sources (eg, household and facility surveys; administrative data), in order to evaluate the effectiveness of MNCH&N policies and programs. Country–led and country–owned, the NEP approach offers a set of core evaluation methods and tools to build national capacity for generating evidence–based answers to program and policy questions. NEP complements and reinforces other ongoing efforts to strengthen country monitoring and evaluation (M&E) systems and to promote data use.

We present the history and rationale underlying NEP, describe core components and work streams supporting NEP implementation in four African countries, and introduce a collection of peer–reviewed articles about NEP to be published in the *Journal of Global Health* over the coming year.

HISTORY AND RATIONALE FOR NEP

The NEP concept took root during an evaluation of the scale–up of Integrated Community Case Management (iCCM) programs in Malawi conducted by the National Statistics Office (NSO) and the Institute for International Programs at the Johns Hopkins Bloomberg School of Public Health (IIP–JHU) with financial support from the Government of Canada [7]. The original evaluation plan was developed in late 2008 using a quasi–experimental pre–post design that compared outcomes in six intervention districts where UNICEF and WHO were supporting iCCM implementation to six comparison districts where no iCCM activities were planned. However, by the end of 2009, iCCM had been scaled–up to all of 28 districts in Malawi with technical and financial support from other partners. With the original comparison districts no longer able to serve in this capacity, the NSO and IIP–JHU evaluation team proposed a "dose–response" design that included all 28 districts in Malawi and aimed to assess whether districts with stronger iCCM implementation had stronger impact. The dose (implementation strength) was measured through newly collected routine and survey data while the response relied on measures of outcome (treatment and intervention coverage) and impact (child mortality) from nationally–representative household surveys that were not specific to the evaluation. The evaluation team coined this approach – using a dose–response analysis with data from combination of sources a *NEP* design. Findings were published in 2016 [8].

In the wake of the Malawi iCCM evaluation redesign, a group of experts in MNCH&N program evaluation published an article in the Lancet that proposed NEP as a departure from the status quo in large–scale effectiveness evaluations [9]. Rigorous evaluations of real–world programs at scale are rare, and those that do happen often focus on a single program area such as HIV or malaria rather than the full MNCH&N continuum of care delivered at health systems and community levels. They tend, like the original Malawi iCCM evaluation, to rely on intervention vs control designs that assume there are comparison areas where no related MNCH&N programs exist and where conditions will be relatively constant across the evaluation period. They typically focus on select subnational areas of interest to specific donors – limiting their utility to national governments who need to make decisions for their entire population. Finally, these approaches can be costly as they often require new data collection across multiple time points [8].

In contrast, the NEP approach articulated by Victora et al. aims to answer evaluation questions that are formulated based on MNCH&N program impact pathways developed using a common framework formulated by Bryce and others [8,9]. Data characterizing the inputs, processes, outputs, outcomes, impacts, and contexts of MNCH&N interventions and programs are assembled to the fullest extent possible from existing survey and routine data sources. The quality of data are assessed and then they are organized by district in a way that facilitates co–analysis and can be expanded as new data become available. NEP analyses are observational. They examine differences across districts (or other sub–national units) for key indicators along the impact pathways using time trends, equity, and regression methods as well as the Lives Saved Tool. NEP is not intended to replace intervention efficacy trials nor does it preclude the need for other types of evaluations. Rather it aims to address the practical needs of LMIC stakeholders for timely evidence to drive high–level MNCH&N policy and program decision making.

IMPLEMENTATION OF NEP FOR MNCH&N

In late 2013, IIP–JHU received funding from Global Affairs Canada (GAC) to take NEP from a concept applied in a single evaluation in Malawi to a sustainable approach to rigorous evaluation by public sector MNCH&N stakeholders in four sub–Saharan African countries–Malawi, Mali, Mozambique and Tanzania. Country–level roll–out began in early 2014. By December 2017, IIP–JHU and government partners in each country aim to build systems and institutional capacity to carry out analyses and communicate NEP findings and to demonstrate that NEP outputs influence decision making by MNCH&N policy and program stakeholders. Activities are organized under three work streams which we highlight below: country–level operationalization; core technical development; and documentation, evaluation and communication.

> The National Evaluation Platform (NEP) is facilitating rigorous use of existing data sources to develop evidence that supports maternal, newborn, child health and nutrition sector decision making by governments in four sub-Saharan African countries.

Public sector institutions lead every aspect of NEP implementation. NEP brings together key government institutions involved in MNCH&N program evaluation, including those that make policies, implement programs, collect and report data, conduct research, and/or oversee budgets. Depending on the country this may include several units under the ministry of health, national statistical offices, multi–sectorial nutrition coordination bodies, ministries responsible for finance and local administration, public universities, and/or public health research institutes. Each country has a designated *NEP Home Institution* with several staff dedicated to NEP oversight and implementation, including data management and stakeholder coordination. A country–specific *NEP High–level Advisory or Steering Committee* is made up of senior leaders from MNCH&N stakeholder institutions in and outside government who guide NEP implementation by recommending or endorsing priority questions and serving as the first audience for NEP findings. The *NEP Technical Task Team* includes staff from each of the country's NEP stakeholder institutions who work in M&E, program coordination or data analytics. The Task Team is the "engine" of NEP, with members working together to develop core evaluation skills, answer evaluation questions and ensure that their respective institutions support and utilize NEP. IIP–JHU has one full–time staff member in each country who coordinates technical assistance, capacity building, and networking. A diverse team of faculty based at Johns Hopkins University (Baltimore, USA) support technical development and implementation along with several external partners including Health Alliance International (Seattle, USA) and 2Paths (Vancouver, Canada).

Country teams adopt a "cycle–based" approach to establishing core NEP systems and building capacity to carry out the evaluation work (**Figure 1**). A cycle is driven by specific evaluation questions identified and prioritized by local MNCH&N stakeholders. Each cycle of NEP development progressively adds new types of data, new analytical skills and new communications approaches to disseminate findings to policy maker and program planner audiences. IIP–JHU has adapted or developed a set of flexible tools to support each step in the NEP cycle including question development, data quality assessment, data management, statistical analysis and communications. For example, the innovative *Stats Report* tool helps ad-

> NEP tools, methods, capacity building materials and lessons learned will be available to support other countries and sectors interested in taking up this approach.
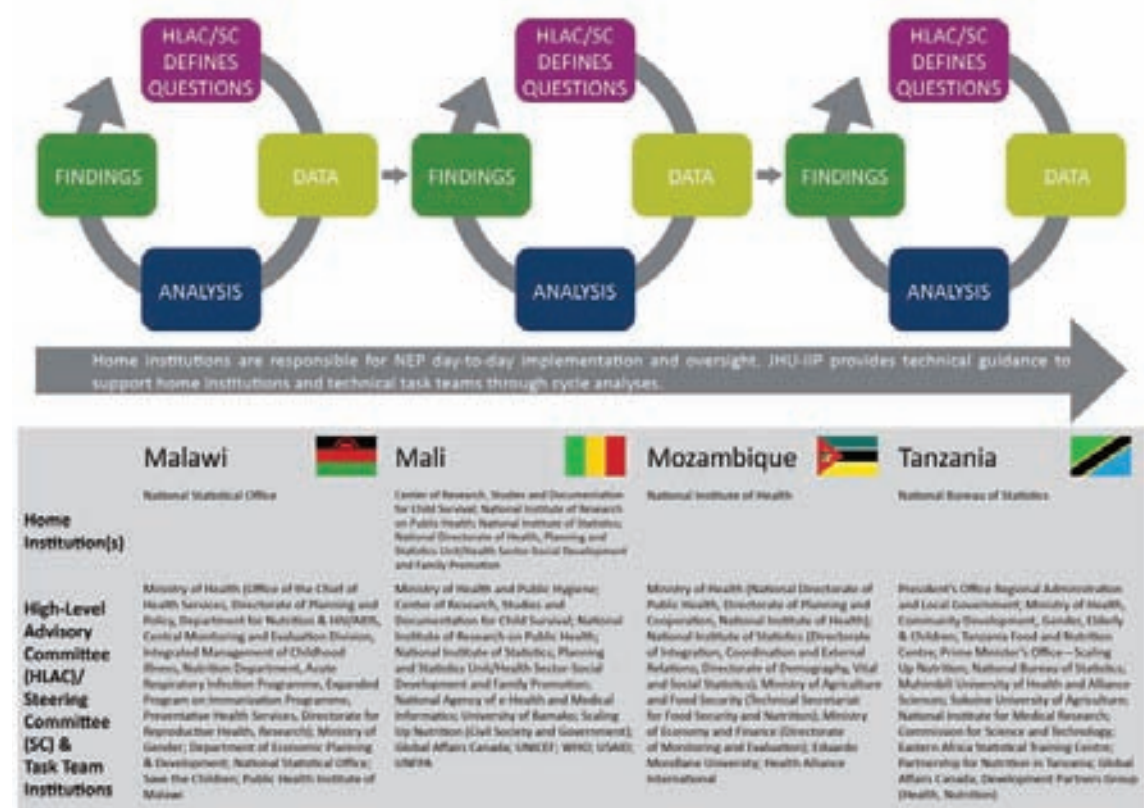
Figure 1. National Evaluation Platform (NEP) structure.

dress limitations in statistical expertise and capacity to use statistical software by allowing users to select, adapt and run core analysis, data management and data quality assessment functions programmed in R using a simple interface. IIP–JHU provides targeted mentorship and curriculum tailored to each country team's existing capacity. The overall NEP curriculum is organized by eight core technical areas that comprise modules to introduce and apply relevant skills. These technical areas include: (1) general evaluation principles; (2) core data concepts; (3) data mapping; (4) data quality assessment; (5) data management; (6) data analysis; (7) new data collection; and (8) interpretation & reporting. Learning modules are designed to be customized and used by other groups wanting to adopt NEP methods.

The effectiveness of NEP will be judged by the extent to which the evidence produced by country teams is incorporated into decision–making processes for women and children's health and nutrition. There are promising signs of NEP influence across the four countries including in Mali where the first cycle resulted in a call by MOH leadership to harmonize maternal child health plans and targets as well as in Tanzania where cycle 1 results were used to develop the next health sector strategic plan. Overall progress across the four countries is being evaluated by an external partner, FSG Social Impact, and findings are used to improve ongoing NEP roll–out and to arrive at summary judgments of NEP effectiveness. These efforts are complemented by extensive internal documentation by IIP–JHU of the planning, decision making, and implementation process during the four years.

AIMS OF THE COLLECTION

Over the coming year, the *Journal of Global Health* will publish a series of peer–reviewed papers related to NEP. Together the articles in the collection will: 1) describe and demonstrate core NEP design features including innovative methods and tools supporting data quality assessment, data management, data analysis, and capacity building; 2) present analyses produced by NEP country teams in response to locally–prioritized evaluation questions and identify how findings have been used by national MNCH&N stakeholders, and 3) assess whether the project has met high–level objectives including the potential for NEP to be sustained in current countries and successfully replicated and refined by other countries or sectors. Ultimately, we believe that sharing our outputs and overall experience in implementing NEP will encourage dialogue among academics, donors, and policymakers on the need to support governments in using data and developing evidence that guides their MNCH&N decision making.

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Reimagining statistical analysis for evidenced-based policy making: Early experiences using Stats Report

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To help overcome capacity-building challenges in the NEP, we began using an online web application called Stats Report which allows us to spend more time analyzing and interpreting data with workshop participants.

Our experiences suggest that Stats Report is able to aid global health practitioners by allowing them to run their analyses without knowing a statistical programming language, the same way one can drive a car without knowing how the engine works.

Global health decision–makers need tools to more easily obtain, analyze, and use data. In the National Evaluation Platform (NEP), we worked with mid– and high–level government staff to build local capacity for data analysis. With these experiences came challenges in statistical capacity–building and collaboration that are likely to be similar in other contexts.

To address these challenges in the NEP, we used an online web application called Stats Report. Built on the R statistical package, Stats Report allows complex data analysis to be undertaken more easily and collaboratively. We used Stats Report in data analysis workshops with government staff in Malawi, Mali, Mozambique, and Tanzania. Statistical experts from our team prepared analysis code, and in–country workshop participants ran the analyses themselves, without having to adjust code, manipulate files, or download software. Using Stats Report, participants generated a variety of analytical outputs more quickly and more reliably than had been possible in previous workshops. We report the way in which participants used and responded to Stats Report.

Our early experiences suggest that Stats Report is easy to use, increases efficiency for data analysis, and enhances transparency and scientific replicability, which may be useful beyond the NEP. A unique strength is the ability to foster collaboration while encouraging users who first run existing analyses to later develop independent skills and the potential to teach others.

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BACKGROUND

Increasingly in global health, governments, donors, and the public are demanding that decisions be made in response to evidence [1]. For this to happen, decision–makers need skills and resources to obtain and interpret the results of scientific analyses. Yet many government policy–makers around the world, and even technical staff, have not been adequately trained in statistics or data science [2]. Often, analyses are outsourced to external experts who are not aware of the policy context, and not living where policies are implemented [3]. While external support can bridge capacity gaps, ultimately this further separates those who analyze from those who decide [4].

Through the National Evaluation Platform (NEP), the Institute for International Programs at Johns Hopkins University (IIP–JHU) has been supporting mid–level government staff in Malawi, Mali, Mozambique, and Tanzania to gather existing data, assess data quality, conduct statistical analyses, and report key messages to policy–makers [5]. The NEP emphasizes country–owned analyses; local institutions lead and conduct their own program and policy evaluations. A key part of this is building capacity in core statistical concepts so that national staff can analyze their data themselves. An independent evaluation of the NEP suggests increased commitment to high–quality data and scientific outputs among stakeholders [6]. However, in working with NEP members to do self–led data analysis, a variety of barriers came to the fore as we built statistical skills and computer competencies, critically thought about data, addressed software issues, and considered analytical documentation and replicability. Traditional education models for our capacity building purposes proved inadequate.

To help overcome these challenges in the NEP, we began using an online web application called Stats Report. Our initial experiences have been positive. Stats Report allows us to spend more time analyzing and interpreting data with workshop participants. Other policy–makers and scientific collaborators within government and non–governmental organizations may also benefit from using Stats Report. This paper describes our early use of Stats Report, and how it is enabling policy–makers to obtain analytical results more easily than before.

STATS REPORT

Stats Report is an online web application, built on top of the R statistical package, for easy and quick data analysis. Users navigate to a website (http://statsreport.org) and select an analysis from a library of analyses, where an R script [7] and associated data are shared. Results are displayed and downloadable as graphs, tables, text, and maps. No software, other than the user's web browser, needs to be installed on an individual's computer in order to run analyses. The analyses that have been put into Stats Report, can be run online by anyone with access to the internet.

Users of Stats Report are largely either people who write R scripts and set up analyses to make their work accessible, or people who run analyses to obtain results and outputs (eg, statistical tests, tables, graphs, other visualizations). For the first group, Stats Report enables quick and wide dissemination and documentation of analyses, and a mechanism for easier collaboration with non–statistical colleagues. For the second group, Stats Report offers access to analyses that are statistically sound, which can be disseminated or revised. Stats Report facilitates learning and capacity building not only as workshop participants discuss results and decide what to do next with their outputs, but also by offering those who want to expand their analytical skills an opportunity to freely view, copy, edit, and learn from other users' statistical scripts.

Stats Report currently hosts code which functions along the spectrum of data use, including code to: manage, analyze, visualize, share, teach, and collaborate. To manage data, users can merge, clean, and reformat data in a systematic way. To analyze data, users can perform summary or complex statistics, which may be customized through user–specified parameters. To visualize data, users can generate and observe outputs in Stats Report and download them. To collaborate, users can contribute to working versions of

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Photo: Workshop on Stats Report from Mozambique. From the collection of Talata Sawadogo-Lewis (used with permission).

analyses, and run updates without worrying about versioning and IT issues. In all cases, users may use either pre–uploaded data to generate their outputs, or bring their own new data to existing analyses.

COUNTRY–LEVEL USE OF STATS REPORT

As part of the NEP, we conducted multiple data analysis workshops with government staff in Malawi, Mali, Mozambique, and Tanzania. The purpose of these workshops was to analyze local data in response to NEP questions and, at the same time, to increase capacity of the NEP members in attendance. NEP teams within the four countries varied in size (Malawi: 40, Mali: 11, Mozambique: 36, Tanzania: 27), as well as sex ratio, age, and technical ability. These people have backgrounds as health workers, managers, statisticians, economists, IT personnel, researchers, lecturers, and professors. Our goal was to train these colleagues to asses and utilize data for maternal and child health and nutrition program evaluation. In collaboration, we assessed data quality, calculated coverage of interventions, analyzed lives saved due to health interventions, demonstrated statistical concepts such as uncertainty and regression using country data, and applied advanced statistical concepts to questions generated by in–country colleagues.

Initially we tried teaching workshops using Stata, and sharing code and data on secure cloud storage. While this met some objectives, we found that file naming conventions, and folder permissions did not foster institutional knowledge transfer, and some colleagues found accessing and updating analyses challenging. It was difficult for colleagues to rerun an analysis, if a software version or operating system on their computer differed from the one that originally generated the analysis. Additionally, we found that formatting and defaults associated with French and Portuguese accented labelling, for example, were not easy to standardize or maintain on individuals' computers. As the NEP incorporated more statistical work, generating results became time–consuming.

In mid–2016, we began using Stats Report, which has addressed many of these challenges. Stats Report has allowed us to teach workshops with fewer time–taking IT tasks, which can interrupt workshop learning. Outputs appear reliably on all participants' computers, the same way that the analyst prepared them. We can disseminate workshop material more efficiently. If someone encounters a bug in an analysis, we can fix it one time, in real–time, and have participants reload statsreport.org and proceed, rather than waiting until a new version of the code has been installed on everyone's computer. If participants request changes to an analysis, we can implement changes and share updates on Stats Report. Furthermore, R is free, so software licensing is not a concern.

In Mozambique, country stakeholders participated in a workshop to analyze routine data. Participants from the Ministry of Health came to the workshop with data extracted from the national health management information system (HMIS). A statistician prepared simple scripts that graphed variables by month or year, with a linear or polynomial fitted curve overlaid to show the trend over time. Participants uploaded data, selected the analysis, and chose the columns within their data that corresponded to the variables needed for the underlying code to produce trends. Participants generated complex graphs and discussed, downloaded, shared, and copied statistical results into written policy briefs and technical reports. Workshop participants appreciated the ability to generate customized results without needing to adjust code themselves. "The main [advantage] for me is the fact that we don't need to be expert in R language to use Stats Report, the program allows us to do complex analyses in a much easier way" [8].

Members of the Mali task team participated in a workshop on regression. Stats Report was used to illustrate basic principles of linear regression, as well as to prepare complex data sets and results. Workshop

participants first used the simple examples to learn about regression, and later furthered their country–led analysis by obtaining reproducible outputs from more advanced statistical scripts. These participants then spent time meaningfully interpreting their results. Capacity building workshops in the NEP prior to Stats Report had necessarily focused more time during workshops on simply obtaining outputs. As one participant said, "[the advantage of Stats Report is it's] easy to use, and orientation to different results is fast. One can obtain estimates, confidence intervals, P–values, odds ratios, tables and graphs" [8].

Outside of workshops, Stats Report has fostered collaboration and built capacity by providing a way to make results available to countries continuously. Stakeholders in NEP countries request analyses that are written by an IIP statistician. In–country technical teams run the analyses independently, download the generated outputs, and use these results in reports, and as figures in presentations to high–level government stakeholders.

While Stats Report has undoubtedly helped us in our capacity building workshops, there are ways to improve it. Workshop participants have mentioned the need for trainings or guidance, and we recognize that we have had more success introducing Stats Report where new users are given repeated opportunities to interact with it, before incorporating it into their work.

A WAY FORWARD FOR COLLABORATIVE DATA ANALYSIS

Our experiences suggest that Stats Report is able to aid global health practitioners by allowing them to run their analyses without knowing a statistical programming language, the same way one can drive a car without knowing how the engine works.

We started the NEP with a capacity building strategy in which an external facilitator teaches concepts and methods to a group of people (panel a in **Figure 1**). With the advent of Stats Report, a statistician now puts results into Stats Report and workshop participants use Stats Report to generate results for interpretation and discussion (panel b in **Figure 1**). As individuals further develop skills and analyses, they can contribute code for others to use (panel c in **Figure 1**). We hope that Stats Report eventually develops into a community of people who both use and contribute code (panel d in **Figure 1**).

In our experience, the situation in panel a **Figure 1** is often a one–time event, with poor documentation and little hope for sustainability. Panel b in **Figure 1** has facilitated better short–term results than traditional capacity building, and fosters collaboration between multi–disciplinary teams between workshops, which is conducive to longer–term capacity building. The capacity jump from the situation in panel b to that in panel c in **Figure 1** is sizable, however, Stats Report involves the documentation of code, and making results reproducible and accessible such that panel c in **Figure 1** represents what we see starting to happen, when individuals learn to edit existing R code to produce different or additional outputs. Panel d in **Figure 1** shows how we think workshop participants could collaborate beyond the workshop, in the future. A network of advanced users who openly share analytical solutions could find faster and better answers to maternal and child health and nutrition program questions.
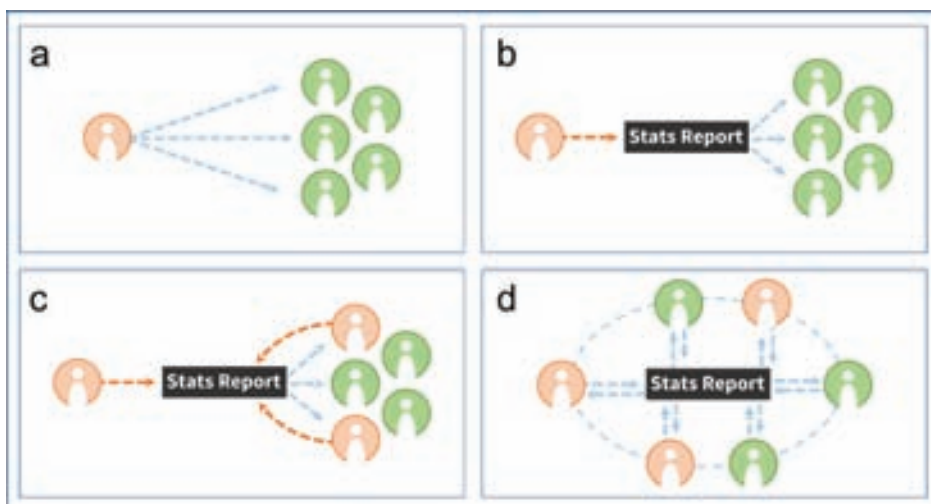
Figure 1. a) traditional model of capacity building, b) capacity building using Stats Report, c) code users becoming code contributors, and d) data analysis in a network of users.

CONCLUSION

To further promote evidenced–based decision–making in global health, we need more accessible and intuitive ways to analyze and use data. We need tools that require minimal training, so people with limited skills can quickly generate valid results, and so institutional capacity is not lost when trained staff leave. Meanwhile, we need people with advanced skills to generate and share results that can be tailored so others can also benefit. When external statistical experts are employed, we need more effective collaboration that builds long–term capacity without creating dependence.

Within the NEP, Stats Report has addressed these needs by providing a user–friendly means for our US–based staff and in–country partners to collaborate. We believe others would similarly benefit from using Stats Report. It helps people analyze data more easily, which is imperative for evidenced–based policy making. It helps people to both run an analysis immediately, and learn from it later. In our experience, Stats Report has been an invaluable way for policy–makers, government staff, and collaborators to better analyze data, and to produce greater evidence.

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VIEWPOINTS

Measuring coverage of essential maternal and newborn care interventions: An unfinished agenda to define the data matrix for action in maternal and newborn health

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Measurement of progress in newborn survival and health during the SDG era requires a comprehensive approach that involves using various sources of data. Data from health management information systems (HMIS) and health facilities will be fundamental for monitoring progress in quality of care which is crucial to meet national and global newborn survival targets.

This collection provides crucial evidence on progress made and outstanding challenges on the road to improving maternal and newborn health using national household data (Demographic and Health Surveys; Multiple Indicator Cluster Surveys) and facility data (Service Provision Assessment) on multi-country coverage of maternal and newborn care seeking and care provision. Of the 11 manuscripts in this collection, six point to the need for more high quality, respectful care provided by health professionals working in enabling environments. Here we consider which data are fit for this improvement purpose.

THE MATERNAL AND NEWBORN MEASUREMENT DYAD

The Sustainable Development Goals have aided the alignment of global strategies across reproductive, maternal, newborn, child and adolescent health. Central to this is recognition that in-service provision as well as measurement it is essential to keep the mother and baby together as a dyad, especially around the time of birth when the majority of maternal and newborn deaths occur. Despite the considerable progress by household and facility surveys to illuminate evidence on the content of care, robust data on quality life-saving care at birth remains scarce in many settings [1-3], and there continues to be a need for global guidance on best measurement methods.

DATA FIT FOR THE PROGRAMMATIC CONTEXT

As practised by disease-specific initiatives such as UNAIDS [4], improving programmes for mothers and newborns requires a combination of data sources. Core indicators from national survey platforms are an essential part of the data matrix, but timely data from delivery rooms that can prospectively inform the decisions of health system actors at multiple levels are also needed. Inevitably this means that well-functioning health management information systems plus civil registration and vital statistics platforms are

Household surveys provide great equity perspective for newborn care. In addition, strengthening health information systems and vital statistics is a critical need of the hour.

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essential, especially when supported by innovations to summarise and visualize these data. Additional platforms may also be needed to provide more granular quality assessments, for example sentinel surveillance in communities and special studies in facilities.

When optimized, these data sources in combination have powerful potential to advance the quality of maternal and newborn care. But defining a complex data matrix alone cannot remove the barrier that poor quality of care poses to maternal and newborn survival: careful guidance is needed to help actors prioritize and organize evidence for action. Considerable work has already been carried out to understand data needs and method limitations [5]. Work is under way to develop guidance on indicators and data collection tools for measurement of maternal and newborn programmes including suggestions for maximizing use of all data sources; however, as research is conducted the guidance will need to be updated and refined to reflect new recommendations. To further accelerate progress now the maternal and newborn health community must work to make sense of when and how each data source can be made to work together.

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Expanding the population coverage of evidence–based interventions with community health workers to save the lives of mothers and children: an analysis of potential global impact using the Lives Saved Tool (LiST)

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Background Evidence has been accumulating that community health workers (CHWs) providing evidence–based interventions as part of community–based primary health care (CBPHC) can lead to reductions in maternal, neonatal and child mortality. However, investments to strengthen and scale–up CHW programs still remain modest.

Methods We used the Lives Saved Tool (LiST) to estimate the number of maternal, neonatal and child deaths and stillbirths that could be prevented if 73 countries effectively scaled up the population coverage of 30 evidence–based interventions that CHWs can deliver in these high–burden countries. We set population coverage targets at 50%, 70%, and 90% and summed the country–level results by region and by all 73 high–burden countries combined. We also estimated which specific interventions would save the most lives.

Findings LiST estimates that a total of 3.0 (sensitivity bounds 1.8–4.0), 4.9 (3.1–6.3) and 6.9 (3.7–8.7) million deaths would be prevented between 2016 and 2020 if CBPHC is gradually scaled up during this period and if coverage of key interventions reaches 50%, 70%, and 90% respectively. There would be 14%, 23%, and 32% fewer deaths in the final year compared to a scenario assuming no intervention coverage scale up. The Africa Region would receive the most benefit by far: 58% of the lives saved at 90% coverage would be in this region. The interventions contributing the greatest impact are nutritional interventions during pregnancy, treatment of malaria with artemisinin compounds, oral rehydration solution for childhood diarrhea, hand washing with soap, and oral antibiotics for pneumonia.

Conclusions Scaling up CHW programming to increase population–level coverage of life–saving interventions represents a very promising strategy to achieve universal health coverage and end preventable maternal and child deaths by 2030. Numerous practical challenges must be overcome, but there is no better alternative at present. Expanding the coverage of key interventions for maternal nutrition and treatment of childhood illnesses, in particular, may produce the greatest gains. Recognizing the millions of lives of mothers and their young offspring that could be achieved by expanding coverage of evidence–based interventions provided by CHWs and strengthening the CBPHC systems that support them underscores the pressing need for commitment from governments and donors over the next 15 years to prioritize funding, so that robust CHW platforms can be refined, strengthened, and expanded.

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The launch of the new Sustainable Development Goals (SDGs) in 2015 [1] gives stakeholders in global health a unique opportunity to acknowledge notable progress, assess current conditions, and designate future priorities. Monitoring of country–specific mortality trends indicates that only a minority of the world's low– and middle–income countries ultimately reached designated Millennium Development Goal (MDG) targets for either MDG 4 (to reduce mortality of children younger than 5 years of age) or MDG 5 (to reduce maternal mortality) [2]. Furthermore, among the Countdown to 2015 (Countdown) priority countries [2], median population coverage for a third of the 21 high–impact maternal and child health interventions remains less than 50%, with notably low coverage of interventions around the time of birth and for managing childhood infection [2].

Devising better approaches to expand coverage of key evidence–based interventions is clearly needed considering that each year 5.9 million deaths still occur among under–5 children [3], 289 000 deaths among women from maternal causes [4], and 2.6 million stillbirths [5], with a majority of these deaths due to preventable or treatable conditions. Accelerating the global rate of reduction of maternal, neonatal and child mortality to end preventable child and maternal deaths remains one of the great unfinished global health agendas of our era. Achieving this will require effective scaling–up so progress can be made toward "universal access to quality essential health–care services," one of the central SDG3 health targets guiding global health development initiatives over the next 15 years [6].

Over the past two decades, evidence has been steadily accumulating that community health workers (CHWs) can play an essential role to deliver many evidence–based interventions for improving maternal, neonatal, and child health (MNCH) [7,8]. CHWs are paraprofessionals or lay individuals from the community, are familiar with the local context, and likely have an in–depth understanding of the indigenous culture. CHWs have typically received a standard training on specific topics of shorter duration than health professionals and they work within their village posts at household and community level to promote healthy behaviors and provide basic services [9]. CHWs and community–based services are increasingly gaining recognition as valuable contributors, because they can effectively expand access to and delivery of health services as well as promote healthy household behaviors, particularly for mothers and children [10]. In addition to direct delivery or provision of services, CHWs can play an essential role by increasing demand for services, serve as key linkages to facility–based interventions, or raise health awareness via promotion or advocacy in communities with limited resources [7]. Many Countdown countries with notable progress for MDGs 4 and 5 have strong national CHW programs [8]. CHW programs may be comprised of health workers acting as volunteers or paid civil servants, or in a capacity somewhere in between these two extremes. Mobilizing a strong and effective health workforce to strengthen health systems and accelerate gains toward universal health coverage was highlighted as a vital priority by the World Health Assembly in 2016 [11].

In this paper, we estimate the impact of MNCH outcomes, if CHWs were able to expand the population coverage of evidence–based interventions across the continuum of care through community–based programming. Our analysis estimates the numbers of deaths that could be prevented in 73 Countdown countries if coverage of these life–saving MNCH interventions were expanded by CHW cadres as a result of robust capacity building and enhanced training to complement services provided at facilities.

METHODS

We identified evidence–based interventions included in the community platform (excluding sexual and reproductive health interventions) as defined for the *Disease Control Priorities Volume 2* [12]. The community platform consists of all evidence–based interventions that can be delivered by locally based CHWs or by outreach CHWs for child health days when immunizations, vitamin A, and other interventions are given. Evidence to support the effectiveness of these interventions is available elsewhere [7,13]. As shown in **Figure 1**, the listed interventions span across a continuum of care from pre–pregnancy care to the prevention and treatment of childhood diseases. Our theory of change assumes that adequate numbers of CHWs could be trained and supported in order to effectively deliver these key interventions in the community. We did not estimate the potential benefit of other activities often carried out by CHWs, such as promoting utilization of health care facilities, educating about family planning or other healthy behaviors, and fostering empowerment.

We used the Lives Saved Tool (LiST), a data–driven modeling platform, to estimate the number of lives that could be saved by reducing the risk of death through the expansion of CHW–led population coverage of specific evidence–based health interventions [14].

Details about the LiST methodology have been described elsewhere [15]. Briefly, LiST estimates country–specific maternal, child, and pregnancy outcomes based upon changes in population–level coverage of interventions while taking into account that country's underlying health status, cause–specific mortality distribution, and the best available estimates of intervention effectiveness using a linear deterministic model. As a module within the Spectrum package, LiST has linkages for parameters including demography, fertility determinants, and HIV/AIDS interventions. Data about population–level coverage for each intervention, defined ideally as the proportion of women and children in need of life–saving intervention who actually receive it [16], are abstracted from the most recent nationally–representative household surveys and sources included the Demographic and Health Surveys (DHS), Multiple Indicator Cluster Surveys (MICS), and other nationally–representative household surveys.

LiST was applied at the country level to calculate the number of deaths that would be averted in Countdown countries if coverage of each CHW–provided intervention was expanded to reach at least 50%, 70% or 90% in the target population. Mexico and China were excluded from the analysis due to limited data about intervention coverage and a low under–five mortality rate (<15 deaths per 1000 live births). The final sample included the remaining 73 Countdown countries. Version 5.43 beta19 of LiST was used for all analyses.

Each country was analyzed separately to examine three scenarios of scale up (50%, 70% or 90% targets) for the subset of MNCH interventions in the community platform. The counterfactual was a baseline model for each country which assumed no change in health intervention coverage between 2015 and the end year of 2020. Projected changes in fertility, HIV/AIDS, and demography were available based upon the Spectrum defaults for secular trends. A pattern of linear increase was modeled to reach designated targets by the end year of 2020. If coverage of an intervention was already reported to be equivalent or above the designated coverage target, coverage was maintained at its current level. The difference between the estimated number of deaths that would occur when coverage is expanded to one of the three coverage targets compared to baseline (with no change in coverage) represents the mortality impact (ie, the number of lives saved or stillbirths prevented) attributable to MNCH coverage expansion.

Mortality reduction was examined for mothers, stillbirths, neonates, and children (1–59 months) for 73 countries (see **Online Supplementary Document**), and results were combined to quantify regional and global impact. The mortality impact was estimated cumulatively (for the period from 2016–2020) and for the target year (2020). Mortality rates were projected by country, and mortality risk for each sub–group was calculated by applying weights for 2015–2020 according to the number of births projected by the UN Population Division for this time period.

Figure 1. Evidence–based interventions that can be provided by community health workers that have been included in the Lives Saved Tool calculations.

FINDINGS

If population–level coverage of CHW–provided maternal, neonatal and child health interventions (shown in **Figure 1**) could expand to reach 50% in 2020 (without reducing the coverage level for those interventions already at a higher level of coverage), an estimated total of 3.0 (sensitivity bounds 1.8–4.0) million lives would be saved during the five–year period from 2016 to 2020. If coverage reached 70% and 90%, the cumulative number of lives saved during this time period would increase to 4.9 (3.1–6.3) and 6.9 (3.7–8.7) million, respectively. Neonates and children 1–59 months of age would be the greatest beneficiaries of increased delivery of inter-

ventions at the community level. At the lowest threshold of 50% coverage, one–quarter (27%, 804 470/3 008 900) of the total impact would be among neonates and half (50%, 1 485 650/3 008 900) would be among children aged 1–59 months. A reduction in the number of stillbirths accounts for one–quarter of the impact (23%, 703 470/3 008 900) and the number of maternal lives saved remains relatively small (<1% of the total lives saved). The distribution of relative impact across these MNCH categories was similar for the three levels of coverage expansion which were modeled.

For the target year of 2020 alone, the total number of deaths would be reduced by approximately 32% (compared to the number predicted if population–level coverage of CHW–led interventions remained static) if near–universal coverage (90%) were achieved (Table 1). Targeting lower levels of coverage (50% and 70%) would produce 14% and 23% fewer deaths in 2020, respectively. Declines would be greatest among children during the post–neonatal period (1–59 months) with 19%, 29% or 41% fewer deaths in this age group estimated in 2020 if these three targets, respectively, were achieved. If coverage of key interventions reached half (50%) of the neonates and pregnant women, the estimated reduction in mortality for the year 2020 would be 13% fewer neonatal deaths and 12% fewer stillbirths.

The under–five mortality rate (U5MR) in 2020 would drop 15%, 25%, or 35% if coverage in these Countdown countries were increased to 50%, 70%, or 90% respectively. With scale–up to near–universal coverage (90%), the U5MR is projected to decline to 38 deaths per 1000 live births in 2020 compared to 59 deaths per 1000 live births in 2015 for this weighted sample of 73 countries (Figure 2). The World Health Organization (WHO) regions with the greatest potential for the number of deaths prevented are the African region and South–East Asia region (Figure 3). By expanding coverage to reach just 50% with CHWs in the Countdown countries in just these two regions, 90% of the total maternal deaths preventable globally through the community platform would be prevented, as would 86% of the total stillbirths, 81% of

Table 1. Estimated number of deaths that would be prevented in 2020 if countries expanded the population coverage of evidence–based maternal, neonatal, and child health interventions that community health workers can provide

Type of death	Deaths in 2020 with NO change in intervention coverage (N)	50% coverage		70% coverage		90% coverage	
		Deaths prevented in 2020 (n)	% reduction	Deaths prevented in 2020 (n)	% reduction	Deaths prevented in 2020 (n)	% reduction
Maternal	297 900	6200	2.1%	12 100	4.1%	19 500	6.5%
Stillbirth	2 294 700	280 400	12.2%	420 700	18.3%	565 040	24.6%
Neonatal	2 454 000	311 400	12.7%	510 400	20.8%	704 230	28.7%
Child (1–59 months)	3 125 100	582 300	18.6%	919 400	29.4%	1 295 160	41.4%
Total	8 171 700	1 180 300	14.4%	1 862 600	22.8%	2 583 930	31.6%
Estimated range*		(697 380–1 541 710)	(8.5%–18.9%)	(1 174 010–2 412 070)	(14.4%–29.5%)	(1 735 790–3 197 900)	(21.2%–39.1%)

*Ranges for impact estimates were produced by conducting sensitivity analyses that calculated impact of interventions based upon the highest level of effectiveness reported (upper bound) for all interventions compared to the lowest levels of effectiveness reported for all interventions (lower bound).
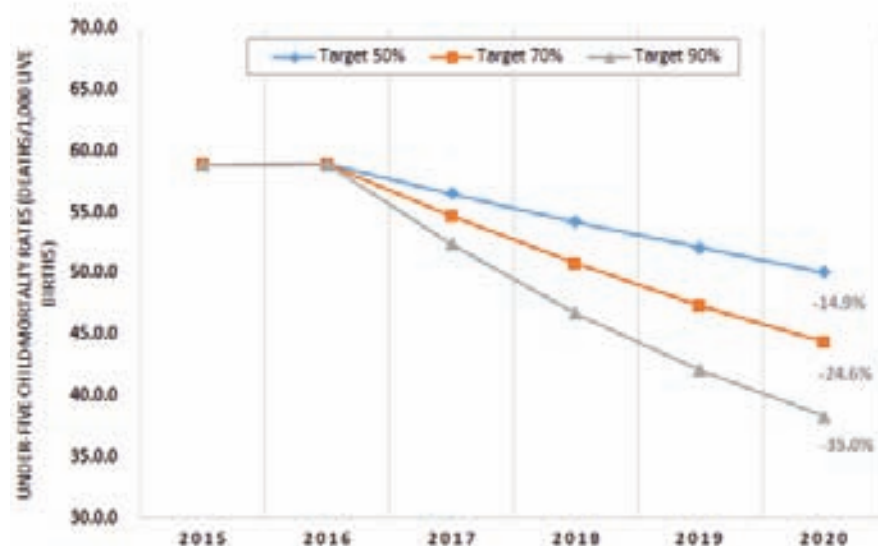
Figure 2. Under–five mortality rate for 73 Countdown countries (weighted by number of births in each country) with intervention scale–up by community health workers to reach population coverage levels of 50%, 70%, or 90%.
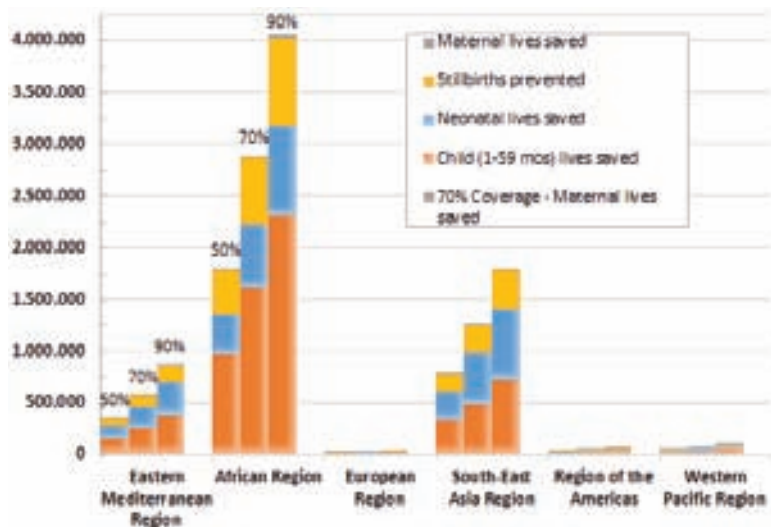
Figure 3. Overall mortality impact (lives saved and stillbirths prevented) by WHO region for 2015–2020 with intervention scale–up by CHWs to reach population coverage of 50%, 70%, and 90%.

the neonatal deaths, and 88% of the child deaths (between 1–59 months). Individual countries that would benefit the most from scaling up community–based interventions to 90% coverage are India (535 000 lives saved nationally), Nigeria (458 000), Pakistan (162 000), and Democratic Republic of Congo (160 000). The **Online Supplementary Document** contains the total numbers of lives saved among mothers, stillbirths, neonates, and children aged 1–59 months by target coverage level.

At a population coverage level of 90%, the specific interventions included in our analyses contributing to save the greatest number of lives for all sub–groups combined are balanced energy and protein supplementation during pregnancy, artemisinin compounds for treatment of malaria, oral antibiotics for pneumonia, oral rehydration solution (ORS) for diarrhea, and multiple micronutrient supplementation during pregnancy (**Figure 4**). Among the interventions that can be provided by CHWs to reduce the risk of stillbirths, improving nutrition during pregnancy played a central role. Balanced energy and protein supplementation and micronutrient supplementation accounted for the majority (49% and 34%, respectively) of the stillbirths prevented. For newborns, one–quarter of neonatal deaths would be prevented by increasing coverage of clean postnatal care (26%) and another one–quarter by implementing thermal care practices (25%). Among all the deaths among children aged 1–59 months that would be prevented by CHW–led scale–up, 19% would be prevented by anti–malarial treatment, 19% by oral antibiotics for pneumonia, and 14% by ORS. Clean birth practices and calcium supplementation during pregnancy provided by CHWs would account for 92% of the maternal lives saved according to our analysis.
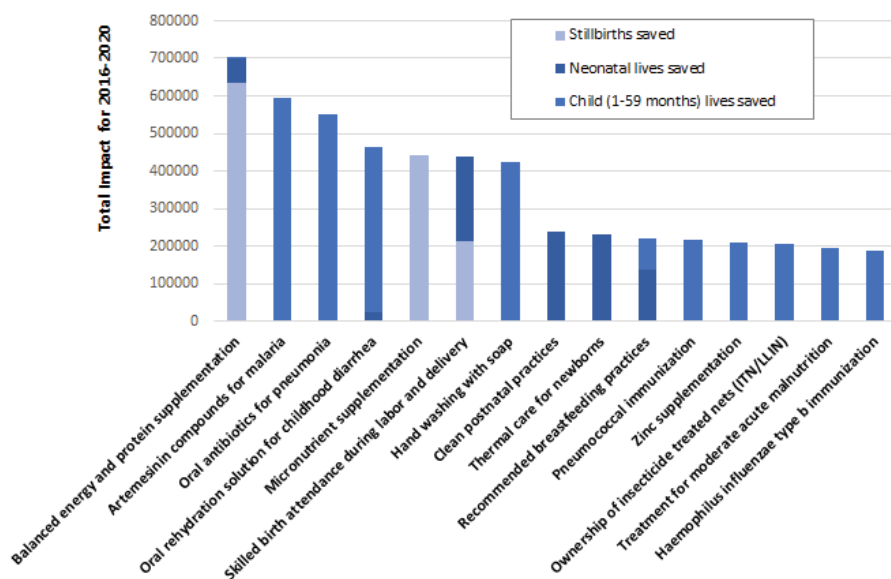
Figure 4. Lives saved and stillbirths prevented by community–based interventions provided by CHWs to reach population coverage of 90% by 2020. The number of maternal lives saved is not shown because the scale of the number is too small to be displayed on the same graph.

DISCUSSION

Our findings indicate that over the next decade and beyond, millions of deaths could be averted by expanding the population coverage of specific evidence–based interventions via well–trained and adequately–supported CHWs. A large portion (32%) of the projected 8.2 million deaths in 2020, including fetal, maternal, neonatal, and child (aged 1–59 months) deaths, would be prevented if near–universal (90%) coverage of key interventions is achieved. With more modest improvements in coverage, the achievements would be notable as well: 23% of deaths would be saved at 70% coverage, and 14% would be saved at 50% coverage.

Evidence of the effectiveness of community–based approaches to improve the health of mothers, newborns, and children in geographically–defined populations is abundant [17,18]. Most assessments have been conducted for a limited subset of interventions (rather than a broader package of interventions) which are implemented in small populations over relatively short periods where CHWs are well–trained, supported, and supervised [18]. Ethiopia and Rwanda are arguably the best recent examples showing the benefits for the health of mothers, newborns, and children by deploying CHWs to expand the population coverage of evidence–based interventions [19,20]. Nonetheless, major challenges remain in achieving high levels of coverage of these interventions, even in Ethiopia [21].

Despite the established benefit of known lifesaving interventions, coverage of essential interventions remains surprisingly low in many settings. In Nigeria, with a population of 31 million children younger than 5 years of age, for example, the population coverage of two highly effective interventions remains abysmally low: only 34% of under–5 children with diarrhea are treated with ORS and only 17% of children younger than 6 months of age are exclusively breastfed [22]. Similar findings exist for other critical interventions in many low–income, high–mortality countries.

Relying exclusively on facility–based platforms (primary health centers and hospitals staffed by doctors and nurses) to end preventable child and maternal deaths and to achieve universal coverage of basic and essential services remains a challenge for several reasons. The utilization of facility–based services decreases exponentially as the household's distance from the location increases, especially if the facility is greater than 3 km or more than 30 minutes away [23]. In many countries, the mean travel time to the nearest facility is more than 30 minutes and in some countries such as Kenya and Ethiopia, considerably more [23]. Construction, staffing, and operating a sufficient number of primary health centers to deliver high–quality care that is readily accessible to the population (within 3 km) and that would be utilized by the majority of the population for the interventions included in our analysis is not achievable in most Countdown countries for the foreseeable future. The logistical and financial challenges are much more daunting than the logistical and financial challenges of building strong CHW programs that complement existing facility–based services.

Existing evidence suggests that using CHWs to deliver essential health services can be a cost–effective approach for health programs in LMICs [24]. Although high–quality community–based programming is not cheap [25], it is the most effective option to reduce mortality (compared to investing solely in facility–based care), as well as the least expensive option we currently have (compared to investing solely in facility–based care) to end preventable child and maternal deaths in resource–limited countries by 2030 [26]. Achieving the same level of coverage of evidence–based interventions by expanding only facility–based services with more numbers of highly trained personnel will take decades longer and cost much more compared to the expansion of community–based health care through CHWs [8,27–30]. CHWs would play an important role as part of any health care system, however, we do not underestimate the challenges of recruiting, training, and retaining enough CHWs to achieve near–universal coverage of evidence–based interventions. This is particularly true for countries that are politically unstable and experiencing conflict. Even in countries with well–developed CHW programs (eg, Ethiopia) coverage of a number of evidence–based interventions remains relatively low [21].

However, in our view, the human resources are available in communities to expand the coverage of community–based MNCH interventions. Experience teaches that people with limited education can learn the skills needed to provide these interventions, and there are adequate numbers of people who are eager and willing to serve their community for the purpose of saving lives. The needed trainers and supervisors can be acquired if the financial investment is adequate.

The organizational challenges of scaling up community–based delivery systems globally in order to reach all households on a regular basis will require innovation and commitment. Identifying the population

most at risk and vulnerable subgroup(s) is essential for addressing equity and closing the coverage gap with CHW–led initiatives. Countries such as Brazil, Bangladesh, Ethiopia, Nepal and Rwanda have made major strides to adapt and develop community–based delivery systems with CHW programs, and they have all made major progress in reducing maternal and child mortality [31]. Guidance for addressing the challenges of CHW programming at scale based on these global experiences and others has been compiled and is readily available [32] along with a set of recommendations from an Expert Panel arising from a comprehensive review of the effectiveness of CBPHC programming for improving MNCH [18]. Specifying the details such as how many and what types of CHWs would be needed to achieve and sustain these levels of coverage is beyond the scope of this article.

The strengths of our approach include the use of a validated model that has been used for multi–country assessments [33,34] and draws upon updated country–specific data about mortality and health status to support a global analysis of impact from coverage expansion. Our study has limitations and many relate to the paucity of data available for reliably measuring and tracking change of intervention coverage at a population level. Modelled trends for expanded coverage were drawn as linear increases but more complex patterns due to saturation or synergy effects may emerge and were not examined in our approach. The decision to keep the counterfactual levels of coverage unchanged from baseline levels is a possible methodological weakness of our analysis, but it simplified our work considerably and we had no solid basis for assuming that there would be major secular expansions in coverage of specific interventions barring a major global push of the type we are arguing for in this paper. Furthermore, whatever increases there might be could possibly vary from intervention to intervention and country to country, so accounting for this in our analysis would have been problematic.

Our mortality impact estimates may be somewhat optimistic if effectiveness of certain interventions in LiST is derived from efficacy studies in which interventions are delivered under relatively ideal conditions. On the other hand, our estimates may be considered conservative because we did not estimate or account for the possible benefits of scaling up other community–based interventions, including oral misoprostol for prevention of post–partum hemorrhage, promotion of care seeking for antenatal and delivery care at facilities (highlighted in a recent review [35]), promotion of HIV testing, counseling on prevention of sexually transmitted infections, promotion of immunizations against human papillomavirus and hepatitis B, as well as the promotion and provision of family planning services. The effectiveness of CHWs in scaling up high–quality family planning services – not only oral contraception and condoms but also injectable contraceptives and even subcutaneous implants – has been well–established [36–39] and fewer births can by itself produce a decline in the number of stillbirths and deaths of mothers and neonates by simply decreasing the denominator – the number of pregnant women and newborns. Eliminating the unmet need for family planning alone would reduce maternal deaths globally by 29% simply by reducing the number of pregnancies [40], and increased birth spacing would significantly reduce the risk of death during infancy, particularly among higher–parity mothers [41,42]. The evidence for reducing the number of stillbirths from balanced energy and protein supplementation during pregnancy is not widely known or incorporated into programs, but nonetheless strong [43,44].

Overall, our findings do nonetheless point to the strong benefits of giving priority to strengthening and expanding community–based delivery systems so that the rate of increase in population coverage of evidence–based interventions for mothers, newborns, and children can begin to accelerate. The highest–impact interventions highlighted by our analysis may be used as a starting point to guide prioritization of community–based programming. Recent experience highlights the need to rigorously plan, evaluate, and refine community–based approaches [45].

CHWs can act as not only agents of change who directly provide health care services but also as liaisons who facilitate proper referrals and timely transfer if complications arise to foster an "integrated continuum of care" [7]. There is no "one size fits all" approach to developing, expanding, and strengthening community–based delivery systems. Each country – both the government and civil society – has to fashion approaches that make sense given their human and financial resources, geography, culture, current health system, and epidemiological context. However, learning from successful examples elsewhere can provide the basis for creative thinking and adaptation to fit local circumstances [32,46].

The findings of our study complement those of another recent global MNCH analysis which compared the number of deaths that could be averted by three service delivery platforms: the community platform, the primary health center platform, and the hospital platform [30]. According to this analysis, 21% of the stillbirths, 49% of the neonatal deaths, and 93% of the child deaths that can be averted by delivering currently available evidence–based interventions through a community platform.

Strengthening community–based delivery strategies can provide additional benefits beyond reducing the number of stillbirths and maternal, neonatal and child deaths. Community–based approaches are becoming increasingly important in the prevention, identification, and treatment of HIV infection (and ending the HIV epidemic), tuberculosis, and non–communicable diseases such as hypertension, diabetes, and mental illness as well as medical care of the elderly [8,47,48]. Furthermore, robust CHW programs have the potential to support identification of infectious disease outbreaks early on, with important savings not only in lives but in prevention of economic meltdowns [49].

For decades, CHWs have been seen by many as a second–class temporary solution for second–class citizens and therefore not viewed as viable long–term members of the national health workforce, especially once countries pass through the epidemiological transition and maternal and child health are no longer epidemiological priorities. However, with not only the growing evidence of the effectiveness of CHWs for improving maternal and child health services but also the increasing recognition of the CHW potential for addressing the growing burden of chronic, non–communicable diseases in developing countries [50], as well as in high–income settings such as the United States to address persistent health disparities [8,51], the tide is now shifting toward the view that CHWs are a long–term asset and essential for high–performing health systems everywhere [10].

CONCLUSIONS

The full potential of community–based approaches to improve population health through CHWs is only beginning to be appreciated by the global health community. Better utilization of existing CHWs, establishing new CHW programs where none are now present, expanding the CHW workforce, creating attractive long–term career development opportunities for CHWs, and strengthening the overall quality of CHW programs will all be required to achieve the full potential of community–based programming for mortality reduction. The three specific interventions that could save the most lives by expanding coverage to 90% are balanced energy and protein supplementation for pregnant women, antibiotic treatment of childhood malaria, and childhood treatment of pneumonia. These are high–impact interventions partly because the current levels of coverage are so low (in contrast to, for instance, immunizations, where current levels of coverage are quite high).

If near–universal (90%) coverage of evidence–based interventions for mothers and children were achieved in 73 Countdown countries, 6.9 million lives would be saved during the period from 2016 to 2020, and the overall number of death would be reduced by 41% compared to baseline levels. The full cost of achieving this goal would be far less than the cost of reaching this level of coverage through expansion of facility–based care provided by higher–level providers.

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Gender inequities in curative and preventive health care use among infants in Bihar, India

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Background India has the highest rate of excess female infant deaths in the world. Studies with decade-old data suggest gender inequities in infant health care seeking, but little new large-scale research has examined this issue. We assessed differences in health care utilization by sex of the child, using 2014 data for Bihar, India.

Methods This was a cross-sectional analysis of statewide representative survey data collected for a non-blinded maternal and child health evaluation study. Participants included mothers of living singleton infants (n = 11 570). Sex was the main exposure. Outcomes included neonatal illness, care seeking for neonatal illness, hospitalization, facility-based postnatal visits, immunizations, and postnatal home visits by frontline workers. Analyses were conducted via multiple logistic regression with survey weights.

Findings The estimated infant sex ratio was 863 females per 1000 males. Females had lower rates of reported neonatal illness (odds ratio (OR) = 0.7, 95% confidence interval (CI) = 0.6–0.9) and hospitalization during infancy (OR = 0.4, 95% CI = 0.3–0.6). Girl neonates had a significantly lower odds of receiving care if ill (80.6% vs 89.1%; OR = 0.5; 95% CI = 0.3–0.8) and lower odds of having a postnatal checkup visit within one month of birth (5.4% vs 7.3%; OR = 0.7, 95% CI = 0.6–0.9). The gender inequity in care seeking was more profound at lower wealth and higher numbers of siblings. Gender differences in immunization and frontline worker visits were not seen.

Interpretation Girls in Bihar have lower odds than boys of receiving facility–based curative and preventive care, and this inequity may partially explain the persistent sex ratio imbalance and excess female mortality. Frontline worker home visits may offer a means of helping better support care for girls.

Gender inequities, or the lesser treatment of and opportunities for women and girls relative to men and boys, compromise maternal and child health globally [1–3]. Such inequities are well–documented in India [4–7], which has an overall sex ratio of 919 females per 1000 males [4] Although much of the sex ratio imbalance in India has been attributed to sex–selective abortion [1,8], the country also has the highest rate of excess female infant and child mortality in the world, with 8.8 more female infants dying per 1000 live births than predicted based on global estimates [9]. Gender differences in health care utilization, particularly in the critical first year of life, may be driving this excess mortality for girls in India [10–12].

Gender differences in child health care utilization in India have been documented in multiple forms of health care use [12], but have been largely un-

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derstood from studies of immunization using nationally representative household survey data from India from 1992 to 2006. This work consistently documents significantly lower rates of immunization for girls in both India and Bihar [13–15]. Further, these studies find that the disparity was enhanced for poorer mothers and based on number of siblings, where full immunization was most likely for oldest males and males born after daughters and least likely for girls with older siblings of either sex [15–17]. Although less research has been conducted on other health care utilization in India, that which has been done documents gender inequities in care seeking for infants and children ill with diarrhea, respiratory or other infectious disease [12,18–20], as well as hospital visits and discharge against medical advice [21–23]. Studies from India document that parents provide up to four times the household expenditure for male relative to female infants, due to both non–use of care and use of less costly care for girls (ie, relying on public rather than preferred private providers) [18,24,25]. Much of this research relies on population–based data more than a decade old or reports from individual health centers. As such, population–based research is needed to examine the current state of gender inequity in infant and child health care use. A trajectory of improvement in gender inequity in immunizations was seen in the period of 1992 to 2006 [17], underscoring the need for more recent reports as expansion of immunization and other health programs has proceeded.

Home visits by frontline workers (FLWs) – community health workers (Accredited Social Health Activists or ASHAs), auxiliary nurse midwives, and social welfare workers for children (Anganwadis) – extend public health care reach to marginalized women in low resource settings [26], and have demonstrated effectiveness and cost–effectiveness in reducing neonatal mortality [27–29]. Although FLWs are known to face gender inequities in the course of their work [30], research is lacking on gender inequity among the recipients of FLW services. Such work is particularly needed because a role of such workers is to increase the demand for utilization of essential health services.

The aim of this article is to investigate whether sex of the infant is associated with maternal reports of infant health, health care use, and postnatal home visits from frontline health workers (FLWs) using data from a 2014 statewide representative household survey in Bihar, India, a large state (population 104 million) with high infant mortality (55 per 1000 live births) and sex ratio imbalance (918 females per 1000 males) [31,32]. Considerations of interactions of sex of the child with wealth and birth order are also explored. This work can offer insights into whether and to what degree gender inequities in infant health care seeking persist in Bihar, with the goal of guiding practical and policy solutions on how to address the excess female infant mortality [33] and sex ratio imbalance in India [31].

METHODS

Data for this study were collected in March to June 2014 as the follow–up household survey for evaluation of Ananya, a public health program that supported a combination of supply–side and demand generation efforts to increase maternal and child health care utilization via the public health system in Bihar [34]. Evaluation of Ananya involved a two–armed quasi–experimental design, comparing mothers of infants and children from the eight districts in which the Ananya program was implemented to those from the remaining 30 districts assigned to the standard of care control condition. Although Ananya included both a baseline and one–year follow–up household survey, only the latter assessed neonatal health and health care utilization outcomes for mothers of 0– to 11–month–olds, providing variables for this analysis. Trained female study staff, subsequent to acquisition of written informed consent, collected all data. Details on the study's multi–stage sampling and other procedures are available elsewhere [35].

The response rate for the sample of mothers of children 0 to 11 months in the survey was 87% (n = 11 654) [35]. The sample was further restricted for this analysis to mothers of living, singleton children (n = 11 570). Ethical approval for the original study was provided by India's Health Ministry Screening Committee. Ethical approval for this analysis was provided by the University of California, San Diego.

Measures

Dependent variables focused on health and curative and preventive health care utilization and were taken from India's Demographic and Health Survey, where they had been validated with a comparable study population [36]. *Neonatal illness* was a binary measure determining whether the infant had any symptoms of illness in the first month of life, including loss of interest in breastfeeding, difficult/rapid breathing, feeling cold to touch, drowsy/difficult to arouse, yellowing of the skin or other symptoms noted by the

mother. Neonatal illness was assessed in the subsample of mothers of children aged 1–11 months to allow for completion of the neonatal period (n = 10 836). *FLW advised seeking care* was a binary measure assessing whether FLWs had recommended seeking facility–based health care for the identified symptoms, and *received facility care* was a binary measure assessing whether the sick infant received care from a health worker (either public or private sector) for the identified symptoms; both were assessed only in the subsample of mothers of 1– to 11–month–olds reporting neonatal illness symptoms (n = 1217). *Hospitalization* since birth was a binary measure assessed for all mothers of infants aged 0–11 months with complete data (n = 11 557). Preventive health care use measures included *facility check–up at one month* (binary, assessed in the subsample of mothers of 0– to 11–month–olds with complete data n = 11 557), and *immunizations current* (defined as receipt of BCG and three Polio and DPT doses), assessed for infants 9–11 months old with complete data (n = 1994).

Measures related to FLW postnatal care home visits included *FLW visit within a week,* a binary measure assessed via a single item on whether such a visit occurred within one week of the index child's birth (n = 11 556, all mothers with complete data). The quality of these visits was then assessed for the subsample of women who reported them (n = 1746) by asking if the visit included each of the following binary measures: *FLW discussed baby danger signs, FLW discussed exclusive breastfeeding, FLW discussed KMC* (kangaroo mother care, or exclusive breastfeeding with skin–to–skin contact), and *FLW discussed how to keep baby warm.*

The independent variable was sex of the infant. Covariates included: maternal age (categorized categorized in 5–year increments: 15–19, 20–24, 25–29, 30–34, or as 35 or older for the oldest age category, mother's education (any vs none), urban/rural residence, birth order of index child (1st/2nd/3rd/4th or higher), whether or not the child had a living brother, and whether or not the participant resided in an Ananya focus district. Minority status (scheduled tribe/scheduled caste or Muslim) and wealth index were also included as covariates. In India, historically disadvantaged castes (Scheduled Castes – SC) and indigenous people (Scheduled Tribes – ST), have been recognized by the government as disadvantaged since independence and are accorded special protections and reservations. National data consistently document greater social, economic, and health disparities disadvantaging SC/ST individuals as well as Muslims, India's largest religious minority group [4]. Household wealth index was constructed using principle component analysis using participants' housing and asset information, including house construction materials, drinking water source, toilet type, cooking fuel, household members per sleeping room, electricity supply and household assets (such as television, bicycle, radio, car, mobile phone and others), with coefficients based on a prior year survey. This index was created in quartiles based on the larger study which included mothers of 0– to 23–month–olds; this study was restricted to 0– to 11–month–olds as comprehensive neonatal health data were only available for this subsample. Consequently, quartiles are not evenly distributed for this subsample.

Data analysis

Multivariable logistic regression models adjusting for covariates were employed to investigate associations between sex of child and each study outcome. Covariates were considered based on social and other determinants of child health in India [14,37] and were included in models following the purposeful approach to model selection of Hosmer and Lemeshow [38]. Exploratory analyses also examined the interactions of child sex with wealth, birth order, minority community and mother's age, to assess whether these covariates were potential modifiers of observed gender inequities, based on their observed importance in prior research [16,23,39]. Interactions were added separately to the adjusted model and defined as significant at $P < 0.15$. All analyses were conducted using the *svy* package in Stata SE 14 (Stata Corp, College Station, TX) and estimates make use of probability weights accounting for complex survey design and sampling.

RESULTS

Female infants made up 46.3% (95% CI = 45.0–47.7) of the sample, which corresponds to an infant sex ratio of 863 females/1000 males (95% CI = 817–912) (**Table 1**). Crude logistic regression analyses indicate that a lower share of female infants had symptoms of neonatal illness compared to males (9.8% vs 11.9%; OR = 0.7, 95% CI = 0.6–0.9) and a lower share of female infants had been hospitalized compared to males (1.2% vs 4.9%; OR = 0.4, 95% CI = 0.3–0.6) (**Table 2**). However, compared to boys, girls had lower odds of receiving neonatal health care for identified symptoms (80.6% vs 89.1%; OR = 0.5, 95%

Table 1. Sample characteristics (n=11 570)

Characteristic	Unweighted N	Weighted % (95% CI)*
Gender of infant		
Male	6231	53.7 (52.3–55.1)
Female	5339	46.3 (45.0–47.7)
Infant's age:		
0–2 months	2864	25.0 (23.9–26.2)
3–5 months	3842	33.2 (32.1–34.5)
6–8 months	2862	24.5 (23.3–25.7)
9–11 months	2002	17.2 (16.2–18.2)
Mother's age:		
15–19	443	4.2 (3.5–4.9)
20–24	4898	42.6 (41.1–44.2)
25–29	4302	35.8 (34.4–37.3)
30–34	1372	12.2 (11.3–13.1)
35+	555	5.2 (4.5–6.0)
Wealth index:		
Quartile 1 (Poorest)	3130	28.3 (26.3–30.4)
Quartile 2	2347	21.1 (19.7–22.5)
Quartile 3	2776	24.6 (23.2–26.1)
Quartile 4 (Richest)	3305	26.0 (24.1–27.9)
Mother's education:		
No schooling	5860	52.3 (50.2–54.4)
Any schooling	5710	47.7 (45.6–49.8)
Birth order:		
1st child	3625	31.2 (29.8–32.6)
2nd child	3275	27.6 (26.4–28.9)
3rd child	2274	20.1 (19.0–21.1)
4th child or higher	2396	21.2 (19.9–22.5)
Minority community designation:		
Scheduled Caste/Scheduled Tribe	2979	26.1 (23.7–28.7)
Muslim	2026	17.3 (14.6–20.3)
Neither	6565	56.6 (53.7–59.5)
Area of residence:		
Urban	2135	10.3 (8.5–12.5)
Rural	9435	89.7 (87.5–91.5)
Ananya District:		
Yes	3072	24.2 (21.4–27.2)
No	8498	75.8 (72.8–78.6)
Child has a living brother:		
Yes	5135	44.4 (42.8–46.1)
No	6434	55.5 (53.9–57.2)

*Weighted % uses probability weights based on survey design and sampling. CI – confidence interval.

CI = 0.3–0.8) and of receiving preventive care at a facility at 1 month (5.4% vs 7.3%; OR = 0.7, 95% CI = 0.6–0.9). Gender differences were not seen in immunizations, FLW postnatal visits or FLW advice to seek care. However, neither immunizations nor FLW visits occurred at target levels. Receipt of all immunizations (BCG, Polio 3 and DPT 3) by nine months was 59.9% for girls and 62.2% for boys. Only 16% of girls and boys had received a postnatal care home visit from an FLW in the first week post–partum. Multivariable analyses yielded similar association findings, with girls having lower odds than boys of having health concerns but also lower odds of receiving curative or preventive neonatal care (**Tables 3** and **4**). No effects of sex were seen on FLW visits.

Stratum–specific odds ratios for interactions between sex of child and birth order, as well as sex of child and wealth, are presented in **Table 5** for outcomes associated with child sex in the primary analyses and demonstrating significant interaction effects ($P < 0.15$). Only receipt of care for neonatal illness met these criteria. In the case of birth order modifying the effect of sex on receipt of care for neonatal illness, there was no difference among firstborn children but an increasing disparity for females with higher birth order. This culminated in girls having 90% reduced odds of receiving care relative to boys when restricting to fourth or higher child (adjusted OR (aOR) = 0.1, 95% CI = 0.1–0.3). Wealth index also demonstrated significant effect measure modification with child sex in the model predicting receipt of care for neonatal symptoms. The gender inequity disfavoring females was most pronounced among the poorest quartile; similarly, the disparity between highest and lowest quartiles of wealth was more pronounced among females than males. Among the lowest wealth quartile, girls' odds of receiving care were 80% reduced relative to boys (aOR = 0.2, 95% CI = 0.1–0.5). Similarly, among females, those in quartile 1 had lower odds of this outcome relative to those in quartile 4 (OR = 0.3; 95% CI = 0.1–0.7); this association of wealth with receiving neonatal care did not hold among males.

DISCUSSION

Results of this study document significant gender inequities in indicators of curative and preventive neonatal health care use, with girls having lower odds than boys to receive care for neonatal illness and facility–delivered postnatal wellness care. Moreover, observed gender inequity in neonatal care seeking is more pronounced among infants with a larger number of siblings and among households in the poorest wealth quartile, conditions likely associated with a relative scarcity of household resources. These findings indicate that, as seen in smaller scale and older studies from India [18,21,24], gender bias continues to affect parents' health care seeking for the child, and these effects are exacerbated when household resources are limited or over–extended. FLW visits, although currently at low numbers, encouragingly do not exhibit the same bias.

Despite the greater odds of non–receipt of care, girls had lower odds of being reported ill during the neonatal period compared to boys. This finding corresponds with national indications of lower risk of neonatal death for girls relative to boys, suggesting greater biologic vulnerability for boys relative to girls [9]. The odds of hospitalization in the first year of life, a more rare and expensive event, differed even more starkly between boy and girl infants, and as with neonatal illness, may be attributable to biology. However, it may also, at least in part, be attributable to greater use of hospitalization when needed for boys

Table 2. Prevalence of illness, curative care, preventive care and frontline health worker measures by sex – bivariate analysis

HEALTH OR HEALTH CARE MEASURE	MALE PREVALENCE		FEMALE PREVALENCE		ASSOCIATION OF FEMALE SEX WITH HEALTH MEASURE	
	Weighted % (95% CI)	Unweighted n	Weighted % (95% CI)	Unweighted n	OR (95% CI)*	P†
Symptoms of neonatal illness‡	12.9 (11.6–14.5)	723	9.8 (8.5–11.2)	494	0.7 (0.6–0.9)	0.001
FLW advised seeking care for neonatal illness§	16.8 (12.7–21.8)	113	19.0 (13.2–26.5)	84	1.2 (0.7–2.0)	0.58
Received care for neonatal illness§	89.1 (85.5–92.0)	634	80.6 (75.3–85.0)	397	0.5 (0.3–0.8)	0.003
Hospitalization	4.9 (4.1–5.8)	283	2.2 (1.8–2.8)	139	0.4 (0.3–0.6)	<0.001
Facility checkup at one month	7.3 (6.2–8.6)	465	5.4 (4.5–6.6)	311	0.7 (0.6–0.9)	0.01
Immunizations current at 9 months‖	62.2 (57.6–66.2)	677	59.9 (55.1–64.5)	59	0.9 (0.7–1.2)	0.52
FLW postnatal visit within a week	16.3 (14.6–18.2)	940	16.2 (14.6–18.0)	805	1 (0.9–1.2)	0.95
FLW discussed baby danger signs	30.8 (26.6–35.3)	281	30.0 (24.7–35.8)	261	1 (0.7–1.3)	0.80
FLW discussed exclusive breastfeeding	81.3 (77.2–84.7)	763	78.1 (72.7–82.8)	638	0.8 (0.6–1.2)	0.32
FLW discussed KMC	41.5 (36.8–46.5)	396	40.3 (34.9–46.0)	333	1 (0.7–1.2)	0.71
FLW discussed how to keep baby warm	39.3 (34.0–44.9)	371	37.3 (32.1–42.9)	315	0.9 (0.7–1.3)	0.63

CI – confidence interval, OR – odds ratio, FLW – frontline health worker, including community health workers (ASHAs), auxiliary nurse midwives, and social workers for children (Anganwadis), KMC – Kangaroo Mother Care

*Odds ratios are for females relative to males from simple logistic regression of the specified health/health care measure on sex

†All P values and 95% confidence intervals reflect Wald tests from simple logistic regression using probability weights based on survey design and sampling

‡Subsample of postneonatal infants (≥1 to 11 months old).

§For subsample of post–neonates who had experienced neonatal illness.

‖Subsample ≥9 months old; Immunizations current defined as having received Bacille Calmette–Guérin (BCG), 3 doses polio and 3 doses DPT (Diphtheria, Pertussis and Tetanus).

relative to girls. As noted previously, research from India documents that higher–cost medical care, such as hospitalization, is more likely to be prioritized and used when needed for boys relative to girls [18,24,39], while discharge against medical advice is more likely for girls relative to boys [21].

Importantly, immunization coverage did not differ by infant sex at 9 months, a finding contrary to a number of studies conducted in India in the past [13–16]. These findings suggest that the growing efforts to maximize immunization coverage since 2006–2007 – when much of the data on gender disparities in immunization were collected – are not only expanding coverage but also reducing gender inequities [40]. Of note, these improvements were based on access to care broadly and not on addressing underlying causes of gender inequities in immunization uptake. Consequently, ongoing gender inequities in use of other health services persist, suggesting that improving access, while important, will be inadequate to address observed gender inequities in care. More work is needed to identify how to work more effectively with parents to increase their value for their girl children, particularly in the presence of older children and male children. Reinforcing this point is a recent analysis of infant and child mortality in neighboring Odisha state, which indicated that while infant and child mortality significantly decreased from 2006 to 2012, the trend was not observed for girls [41].

A related paradox of extending health programs to combat social inequalities in health is that boys have greater access to these facility–based services than do girls [33]. Use of FLWs via home visits may provide an opportunity to extend reach to girls more effectively, particularly for those from more vulnerable impoverished households [26]. Study findings suggest no gender bias in FLWs' provision of a postnatal visit or advice for child health care seeking. Unfortunately, too few women received a FLW postnatal visit, only 16%. This is particularly disappointing given the promise FLWs offer to help address parents' gender bias in care seeking. A post hoc analysis from these data showed a non–significant trend ($P = 0.09$) indicating that girl infants who were advised to seek care by an FLW had a higher odds of having received care compared to girls not so advised (89.4% vs 78.6%; OR = 2.3, 95% CI = 0.9–6.2). This association did not hold among boys, who had higher overall levels of care seeking. Together, these findings suggest that improving coverage of FLW services could play a role in alleviating the gender inequity in care–seeking for infants alongside efforts to improve standing of the girl child.

In addition to findings related to gender inequities and health, some findings regarding social inequities were also observed. Adolescent and Muslim mothers had higher odds of having a sick neonate, and among those with a sick neonate, Muslims had lower odds of having a front line worker (FLW) recommend that they seek care for their infant. Interestingly, there was a higher odds of FLWs recommending care for sick infants more to SC/ST and rural mothers, suggesting that FLWs do support care for more socially vulner-

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Table 3. Associations between sex of the child and illness, curative care and preventive care use – multivariable models

Characteristic	NEONATAL ILLNESS (n=10836)*		FLW advised seeking care for neonatal illness (n=1217)†		RECEIVED FACILITY CARE FOR NEONATAL ILLNESS (n=1217)†		HOSPITALIZATION (n=11557)		FACILITY CHECKUP AT 1 MONTH (n=1557)		IMMUNIZATIONS CURRENT AT 9 MONTHS (n=1994)‡	
	aOR (95% CI)	P§	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
Female sex vs. male	0.7 (0.6–0.9)	0.001	1.2 (0.7–2.0)	0.52	0.5 (0.3–0.8)	0.004	0.4 (0.3–0.6)	<0.001	0.7 (0.6–0.9)	0.02	0.9 (0.7–1.2)	0.52
Mother's age:												
15–19	2.2 (1.1–4.2)	0.02	1.1 (0.2–7.5)	0.90	1.4 (0.3–6.7)	0.71	1.7 (0.6–4.5)	0.32	0.8 (0.4–1.6)	0.56	0.7 (0.3–1.8)	0.47
20–24	1.4 (0.8–2.3)	0.21	1.1 (0.3–3.9)	0.94	0.6 (0.2–2.1)	0.44	1.1 (0.5–2.3)	0.82	0.8 (0.5–1.4)	0.50	1 (0.5–1.9)	>0.99
25–29	1.1 (0.7–1.7)	0.71	1.1 (0.3–3.7)	0.93	0.7 (0.2–2.1)	0.49	1.2 (0.6–2.4)	0.58	0.8 (0.5–1.4)	0.45	0.8 (0.5–1.5)	0.55
30–34	1.3 (0.8–2.1)	0.30	0.8 (0.2–2.8)	0.69	0.9 (0.3–3.2)	0.90	1.2 (0.6–2.5)	0.66	1 (0.6–1.8)	0.87	0.8 (0.4–1.6)	0.59
35+	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Wealth index:												
Quartile 1 (Poorest)	0.9 (0.7–1.3)	0.63	0.4 (0.2–0.8)	0.01	0.5 (0.3–1)	0.04	0.4 (0.2–0.7)	0.001	0.7 (0.5–1.1)	0.10	0.6 (0.4–0.9)	0.02
Quartile 2	1.1 (0.8–1.5)	0.68	0.6 (0.2–1.3)	0.17	0.6 (0.3–1.2)	0.16	1 (0.6–1.5)	0.89	1 (0.7–1.5)	0.93	0.8 (0.5–1.2)	0.24
Quartile 3	1.0 (0.8–1.2)	0.69	0.8 (0.4–1.6)	0.51	0.8 (0.5–1.4)	0.49	0.9 (0.6–1.3)	0.47	0.9 (0.7–1.2)	0.54	0.8 (0.6–1.2)	0.28
Quartile 4 (Richest)	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Mother's education:												
No schooling	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Any schooling	1.2 (0.9–1.5)	0.14	0.8 (0.5–1.3)	0.37	0.8 (0.5–1.4)	0.49	1.5 (1.0–2.1)	0.03	1.5 (1.2–2.0)	0.002	0.9 (0.7–1.2)	0.49
Birth order:												
4th child or higher	1.1 (0.8–1.6)	0.62	0.7 (0.3–1.8)	0.45	0.9 (0.4–2.1)	0.83	1.2 (0.6–2.2)	0.57	0.7 (0.4–1.1)	0.12	1 (0.6–1.7)	0.96
3rd child	1.0 (0.7–1.4)	0.95	0.9 (0.4–2.1)	0.88	1.1 (0.5–2.7)	0.81	0.8 (0.5–1.4)	0.50	0.7 (0.5–1)	0.05	1.3 (0.8–2)	0.27
2nd child	0.8 (0.6–1.1)	0.10	0.8 (0.4–1.7)	.61	1.3 (0.7–2.5)	0.41	1 (0.7–1.4)	0.92	0.9 (0.6–1.2)	0.34	1 (0.7–1.4)	0.97
1st child	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Minority community:												
Scheduled Caste/Scheduled Tribe	1 (0.8–1.3)	0.79	1.7 (1.1–2.9)	0.03	1.1 (0.6–1.8)	0.77	1.1 (0.8–1.5)	0.68	0.9 (0.7–1.2)	0.36	0.8 (0.6–1.2)	0.31
Muslim	1.4 (1.1–1.9)	0.02	0.4 (0.2–0.8)	0.01	1.3 (0.7–2.4)	0.34	1 (0.7–1.4)	0.90	0.9 (0.7–1.3)	0.63	0.7 (0.5–1)	0.03
Neither	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Area of residence:												
Urban	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Rural	1.1 (0.8–1.4)	0.58	2.3 (1.2–4.4)	0.01	1 (0.5–1.8)	0.88	1.5 (1–2.1)	0.04	0.8 (0.6–1)	0.10	1.1 (0.9–1.5)	0.40
Ananya District:												
Yes	1.2 (1.0–1.5)	0.05	1.3 (0.7–2.2)	0.39	0.7 (0.4–1)	0.05	1.5 (1.1–2.1)	0.01	2.2 (1.6–2.9)	<0.001	0.9 (0.7–1.2)	0.48
No	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Child has a living brother:												
Yes	1.1 (0.8–1.4)	0.57	1.2 (0.7–2.1)	0.59	1.1 (0.6–2.0)	0.73	0.6 (0.4–0.9)	0.01	0.8 (0.7–1.1)	0.14	1 (0.7–1.4)	0.91
No	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	

aOR – adjusted odds ratio, CI – confidence interval, Ref. – reference, FLW – frontline health worker, including community health workers (ASHAs), auxiliary nurse midwives, and social workers for children (Anganwadis).

*Subsample of postneonatal infants (≥1 month old).

†Subsample of post–neonates who had experienced symptoms of illness during the neonatal period.

‡≥9 months old. Immunizations current defined as having received Bacille Calmette–Guérin (BCG), 3 doses polio and 3 doses DPT (Diphtheria, Pertussis and Tetanus).

§All P values and 95% confidence intervals reflect Wald tests from multivariable logistic regression using probability weights based on survey design and sampling.

Table 4. Associations between sex of the child and frontline health worker postnatal home visits – multivariable models

Characteristic	FLW visited within a week postpartum (n=11 556)		FLW discussed baby danger signs (n=1746)*		FLW discussed exclusive breastfeeding (n=1746)*		FLW discussed Kangaroo Mother Care (n=1746)*		FLW discussed how to keep baby warm (n=1746)*	
	aOR (95% CI)	P†	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
Female sex vs. male	1.0 (0.9–1.2)	0.96	1.0 (0.7–1.4)	0.98	0.8 (0.5–1.2)	0.22	1.0 (0.7–1.2)	0.69	0.9 (0.7–1.3)	0.69
Mother's age:										
15–19	2.1 (1.1–3.8)	0.02	1.6 (0.5–5.2)	0.40	0.4 (0.1–1.3)	0.12	1.5 (0.5–4.1)	0.44	1.5 (0.5–4.4)	0.47
20–24	1.4 (0.9–2.1)	0.18	0.8 (0.4–1.9)	0.63	0.5 (0.2–1.1)	0.09	1.1 (0.6–2.2)	0.78	1 (0.5–2.2)	0.96
25–29	1.3 (0.9–2.0)	0.19	1.6 (0.8–3.3)	0.21	0.8 (0.4–2.0)	0.68	2.3 (1.2–4.3)	0.01	1.5 (0.8–3.0)	0.25
30–34	1.4 (0.9–2.1)	0.11	1.9 (0.9–4.4)	0.11	0.9 (0.4–2.2)	0.83	2.5 (1.2–5.1)	0.01	1.3 (0.6–2.9)	0.47
35+	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Wealth index:										
Quartile 1 (Poorest)	0.9 (0.7–1.1)	0.29	0.6 (0.4–1.0)	0.05	0.5 (0.3–0.9)	0.03	0.7 (0.5–1.1)	0.17	0.7 (0.4–1.1)	0.12
Quartile 2	1 (0.8–1.3)	0.92	1 (0.7–1.6)	0.85	1.2 (0.7–2.3)	0.52	1 (0.6–1.6)	0.94	1.2 (0.8–1.8)	0.37
Quartile 3	1.2 (0.9–1.4)	0.18	0.9 (0.5–1.5)	0.66	0.6 (0.4–1.0)	0.04	0.9 (0.6–1.4)	0.80	0.8 (0.5–1.4)	0.47
Quartile 4 (Richest)	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Any education vs. no education	1.1 (0.9–1.3)	0.50	1 (0.7–1.6)	0.93	1.3 (0.8–2.1)	0.22	1.1 (0.8–1.6)	0.48	1 (0.7–1.4)	0.89
Birth order:										
4th child or higher	1.2 (0.8–1.7)	0.35	0.4 (0.2–0.7)	0.001	0.9 (0.5–1.9)	0.86	0.5 (0.3–0.8)	0.009	0.8 (0.5–1.4)	0.41
3rd child	0.9 (0.7–1.2)	0.57	0.3 (0.2–0.6)	0.001	0.9 (0.5–1.8)	0.80	0.7 (0.4–1.0)	0.08	0.8 (0.5–1.4)	0.48
2nd child	0.9 (0.7–1.2)	0.45	0.7 (0.4–1.1)	0.11	0.9 (0.5–1.5)	0.69	0.6 (0.4–0.9)	0.02	1 (0.6–1.5)	0.88
1st child	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Minority community:										
Scheduled Caste/Scheduled Tribe	1.1 (0.9–1.4)	0.32	1.4 (0.9–2.1)	0.14	1.2 (0.7–1.8)	0.54	1.1 (0.8–1.6)	0.57	1.1 (0.7–1.5)	0.76
Muslim	0.9 (0.7–1.2)	0.38	1.2 (0.8–1.8)	0.33	1.2 (0.7–2.0)	0.43	1 (0.7–1.6)	0.84	1.2 (0.8–1.8)	0.32
Neither	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Area of residence:										
Urban	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Rural	2.3 (1.7–3.0)	0.001	0.6 (0.4–1.1)	0.11	0.9 (0.6–1.6)	0.78	1 (0.6–1.7)	0.96	0.6 (0.4–1.0)	0.04
Ananya District:										
Yes	1.2 (1.0–1.5)	0.12	1.1 (0.7–1.7)	0.63	1.3 (0.9–1.9)	0.18	1.4 (1.0–2.0)	0.06	1.5 (1.1–2.1)	0.02
No	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	
Child has a living brother:										
Yes	1.2 (1.0–1.5)	0.03	1.2 (0.8–1.8)	0.34	1 (0.6–1.6)	0.93	1 (0.7–1.4)	0.98	1 (0.7–1.4)	0.93
No	1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]		1 [Ref.]	

aOR – adjusted odds ratio, CI – confidence interval, Ref. – reference, FLW: frontline health worker, including community health workers (ASHAs), auxiliary nurse midwives, and social workers for children (Anganwadis)

*Subsample reporting an FLW postnatal care visit in the first week postpartum.

†All P values and 95% confidence intervals reflect Wald tests from multivariate logistic regression using probability weights based on survey design and sampling.

Table 5. Stratum–specific associations between sex of child and receipt of care for neonatal illness*

Interaction stratum	Main effect	Received care for neonatal symptoms (n=1217)†	
		aOR (95% CI)	P‡
Child sex × birth order:			0.01
4th child or higher	Female vs. male	0.1 (0.1–0.3)	<0.001
3rd child	Female vs. male	0.5 (0.2–1.2)	0.11
2nd child	Female vs. male	0.6 (0.2–1.5)	0.27
1st child	Female vs. male	1.0 (0.5–2.3)	0.92
Female	4th or higher vs. 1st child	0.4 (0.1–1.0)	0.05
	3rd vs. 1st child	0.7 (0.3–2.2)	0.59
	2nd vs. 1st child	1.0 (0.4–2.5)	0.94
Male	4th or higher vs. 1st child	2.6 (0.9–7.0)	0.07
	3rd vs. 1st child	1.6 (0.6–4.4)	0.35
	2nd vs. 1st child	1.7 (0.8–3.8)	0.2
Child sex × wealth index:			0.06
Quartile 1 (Poorest)	Female vs. male	0.2 (0.1–0.5)	<0.001
Quartile 2	Female vs. male	1.2 (0.5–3.0)	0.75
Quartile 3	Female vs. male	0.6 (0.3–1.4)	0.25
Quartile 4 (Richest)	Female vs. male	0.6 (0.3–1.4)	0.25
Female	Quartile 1 vs. 4	0.3 (0.1–0.7)	0.005
	Quartile 2 vs. 4	0.9 (0.4–2.2)	0.75
	Quartile 3 vs. 4	0.8 (0.3–1.8)	0.58
Male	Quartile 1 vs. 4	0.9 (0.4–2.2)	0.85
	Quartile 2 vs. 4	0.5 (0.2–1.1)	0.08
	Quartile 3 vs. 4	0.8 (0.4–1.7)	0.57

aOR – adjusted odds ratio, CI – confidence interval

*In addition to the interaction and main effects, the interaction models included remaining covariates of maternal age, household wealth index, mother's education, birth order of index child, minority community (caste or religion), rural residence, whether or not the participant resided in an Ananya focus district, and whether or not the child had a living brother. Logistic regression models based on the two interactions displayed, birth order and wealth, were tested with an overall Wald test and found to be significant at alpha=0.15. Odds ratios within strata based on those interactions are displayed.

†Subsample of post–neonates who had experienced neonatal illness.

‡All p–values and 95% confidence intervals are from logistic regressions using probability weights based on survey design and sampling.

able groups, but perhaps not evenly. Notably, the poorest infants appear to be the most vulnerable, having lower odds than the richest infants of having a FLW recommend care when ill, to receive care when ill, to be hospitalized, and to receive vaccinations, suggesting that poverty remains a key driver for non–use of health care in Bihar. These findings may help explain the heightened risk for infant mortality among the abject poor in India [42]. Sadly, and as noted above, poverty appears to exacerbate what appears to be gender discriminatory effects on neonatal care utilization.

Some study limitations must be considered. Analyses are cross–sectional, so causality cannot be assumed. The data are self–reported by mothers and thus subject to recall and social desirability biases. Additionally, mortality data were not available for this analysis. Participation biases may exist, and we unfortunately did not collect data on those who declined participation to ascertain what these biases may be; the high participation rate (87%, as noted in the methods) reduces our vulnerability to these potential biases. A key challenge for interpretation of this study and many that investigate gender bias in health care is that some of the important outcomes represent both health need and health care utilization. Differentials in hospitalization of baby boys and girls likely reflect differences in severity of underlying illness, gender bias in parents' use of care or referral systems' recommendations for care. Bhan and colleagues found hospitalization for diarrheal illness in a New Delhi hospital was much lower among girls, but mortality was higher at the same time, undermining differential vulnerability as an explanation [23]. Additionally, symptoms of illness in the first month can reflect perception or actual rates of illness [13]. In our survey, the key question about actual receipt of care, restricted to those who endorsed neonatal illness, shows a marked gender inequity, as does the preventive care outcome of one–month well visits at a facility. These together suggest gender inequity even within the recognized and reported cases of illness and further imply that the same underlying gender bias could contribute to other findings such as the stark difference in hospitalizations. Assessing the presumed effect of health care use on mortality with any possible effect modification by gender would be an important future direction for this research.

CONCLUSION

This study documents significant gender inequities disadvantaging infant girls in the receipt of facility–based curative and preventive health care in Bihar, India, implying a role of gender bias and neglect on the part of parents. Notably, gender inequity in immunization coverage at 9 months of age was not observed, suggesting dramatic improvement on this issue over the past decade [13–17], likely via expansion in local access to vaccinations [40]. Front–line worker visits and services were not implicated in the gender disparity. These findings suggest that focus on gender bias and its impact on parents' health care decision–making remains a concern in Bihar, and inadequate use of health services for girls may be contributing to the excess female mortality rate in the country. Study findings indicate that poverty and a higher number of siblings worsened observed gender inequities and suggest a role for targeting those particularly limited by resources. Broader reach of care beyond the facility, possibly through FLWs and home visits, may offer opportunity to support improvement, but such efforts must coincide with broader social change to support the value of the girl child in India and parents' recognition of this value.

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Association between internalized stigma and depression among HIV-positive persons entering into care in Southern India

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Background In India, which has the third largest HIV epidemic in the world, depression and HIV–related stigma may contribute to high rates of poor HIV–related outcomes such as loss to care and lack of virologic suppression.

Methods We analyzed data from a large HIV treatment center in southern India to estimate the burden of depressive symptoms and internalized stigma among Indian people living with HIV (PLHIV) entering into HIV care and to test the hypothesis that probable depression was associated with internalized stigma. We fitted modified Poisson regression models, adjusted for sociodemographic variables, with probable depression (PHQ–9 score ≥10 or recent suicidal thoughts) as the outcome variable and the Internalized AIDS–Related Stigma Scale (IARSS) score as the explanatory variable.

Findings 521 persons (304 men and 217 women) entering into HIV care between January 2015 and May 2016 were included in the analyses. The prevalence of probable depression was 10% and the mean IARSS score was 2.4 (out of 6), with 82% of participants endorsing at least one item on the IARSS. There was a nearly two times higher risk of probable depression for every additional point on the IARSS score (Adjusted Risk Ratio: 1.83; 95% confidence interval, 1.56–2.14).

Conclusions Depression and internalized stigma are highly correlated among PLHIV entering into HIV care in southern India and may provide targets for policymakers seeking to improve HIV–related outcomes in India.

To help end the worldwide AIDS epidemic by 2030, the Joint United Nations Programme on HIV/AIDS proposed a set of Fast Track or "90–90–90" targets to be achieved by 2020: the diagnosis of 90% of all people living with HIV (PLHIV), the provision of antiretroviral therapy (ART) to 90% of those diagnosed, and the achievement of an undetectable viral load for 90% of those on treatment [1]. India, which has the third largest HIV epidemic in the world with 2.1 million PLHIV [2], has dramatically scaled–up access to ART over the last decade [3,4]. However, high rates of loss to HIV care suggest that India is far from achieving the 90–90–90 targets. In one cohort study in Andhra Pradesh, only 31% of patients diagnosed with HIV ultimately achieved virologic suppression [5]. Similarly, the overall drop–out rate at a large HIV care center in Tamil Nadu was 38 per 100 person–years [6]. Finally, in a nationwide cohort of men who have sex with men (MSM) and people who inject drugs (PID), only 10% of HIV–infected cohort participants were on ART and virologically suppressed [7]. These estimates suggest that India is far from achieving the goal to eliminate AIDS.

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Little is known about the reasons for loss to HIV care in India after diagnosis. One study of loss to HIV care focused on clinical predictors such as CD4$^+$ cell count and weight [8]. More recently, a study of Indian MSM and PID found that certain clinic–based factors, failure to disclose one's serostatus to others, and depressive symptoms were associated with decreased odds of linkage to HIV care [9]. Beyond this study, little is known about how psychosocial factors such as depression and HIV–related stigma affect loss to HIV care in India.

In other settings, particularly in sub–Saharan Africa, HIV–related stigma has been associated with psychological distress and depression [10,11] and poorer ART adherence among PLHIV [12,13]. Similarly, depression among PLHIV has been associated with increased transmission risk [14,15], greater CD4$^+$ count declines [16,17], reduced ART adherence [18], and more rapid progression to AIDS and death [17,19,20]. Importantly, depression is a modifiable risk factor, as treatment of depression can result in reduced risk of HIV transmission [21] and improved ART adherence and virologic suppression [22]. Some studies have suggested that depression treatment should be combined with behavioral interventions to maximize improvements in HIV–related outcomes [23–25].

Compared to other low– and middle–income countries (LMICs) in which stigma and depression have been studied more extensively (eg, countries in sub–Saharan Africa), India features a markedly different socio–cultural environment and an epidemic that is highly concentrated among female sex workers, MSM, and PID [2]. As such, one cannot assume that findings on stigma and depression from other LMICs are applicable to the Indian context. Both HIV–related stigma [26–28] and depression [29–31] have been found to be highly prevalent among Indian PLHIV. Although some studies have shown an association between stigma and depression among Indian PLHIV [26,32,33], these studies included PLHIV both in and out of care at ART centers. If stigma and depression inhibit PLHIV from seeking care or contribute to loss to care after enrollment, then estimates based on mixed samples could potentially overstate the association between stigma and depression. Understanding the association between stigma and depression specifically among PLHIV entering into HIV care is particularly important, as this step in the HIV care continuum represents an opportunity to initiate interventions to attenuate their potential negative effects on HIV–related outcomes. If stigma and depression are closely correlated among PLHIV entering into care and initiating ART, then multi–faceted behavioral interventions targeting both depression as well as drivers of stigma may be needed to keep these PLHIV in care and virologically suppressed.

To help address these gaps in knowledge, we conducted a study of adults entering into care at a large HIV treatment center in Chennai, India. We hypothesized that *internalized stigma* (the internalization and acceptance of negative attitudes towards PLHIV and subsequent development of self–defacing beliefs [34]) and *depression* would be highly prevalent in this population and that internalized stigma and depression were highly correlated. The aims of this study were to 1) estimate the burden of internalized stigma and depression and 2) estimate the association between internalized stigma and depression.

METHODS

Study setting and procedures

This cross–sectional study was conducted at the Y.R. Gaitonde Centre for AIDS Research and Education (YRG CARE) in Chennai, India. YRG CARE is one of the largest private organizations providing HIV care in India, having treated over 20 000 PLHIV since its founding in 1993. Chennai is the capital of Tamil Nadu state and one of the epicenters of the HIV epidemic in India [35]. As in other areas of India, the HIV epidemic in Tamil Nadu is concentrated, with an overall prevalence of 0.31% but a higher prevalence among female sex workers, MSM, and PID (between 2.4% and 9.5%) [2,36,37]. The majority of patients at YRG CARE come from Tamil Nadu and Andhra Pradesh states. Most patients at YRG CARE self–identify as heterosexual [29], as there are other organizations in Chennai which are perceived as specializing in care for sexual and gender minorities.

Patients were eligible for participation in the study if they were at least 18 years of age, HIV–infected, and newly entering into HIV care at YRG CARE between January 2015 and May 2016. Interviews were about 20 minutes long and were conducted by one of two female HIV counselors in the patient's preferred language (Tamil, Telugu, or English). All study materials were written in English, professionally translated into Tamil or Telugu, and back–translated to English to ensure fidelity to the original. Study staff obtained signed, or in case of illiteracy, thumbprint–marked informed consent documents from all participants. No remuneration was given. Potential participants were informed both verbally and through informed

consent documents that refusal to participate would not impact the care that they would receive. Ethical approval for study procedures was obtained from the Institutional Review Boards of Fenway Health (Boston, Massachusetts, USA) and YRG CARE.

Measures

We administered questionnaires to PLHIV at their first clinical visit to YRG CARE after HIV diagnosis. To assess for depressive symptoms, we included the Patient Health Questionnaire–9 (PHQ–9) [38,39], which has been previously translated into Tamil and Telugu and validated in India [40,41]. Higher PHQ–9 scores (range, 0–27) signify greater levels of depression symptom severity. Study participants were considered to screen positive for probable depression if they either 1) returned a PHQ–9 score of greater than or equal to 10 or 2) endorsed the item "thoughts that [one] would be better off dead or of hurting [one]self in some way", as recommended by Kroenke and Spitzer [42].

To measure internalized stigma, we included the six–item Internalized AIDS–Related Stigma Scale (IARSS) [43]. We chose to focus on internalized stigma given a growing consensus that internalized stigma is an important predictor of HIV–related outcomes [44]. The IARSS is the most commonly used measure of internalized stigma in the literature, has been validated in multiple settings [45,46], and is relatively brief compared to other commonly–used stigma scales such as the Berger HIV Stigma Scale [47] and the HIV/AIDS Stigma Instrument – PLWA [48]. Two items relate to concerns about disclosure and four items relate to feelings of shame and/or self–hatred (Table 1). Responses were elicited on a binary scale (yes/no); scale scores represent the sum total of endorsed items (range 0–6). Like most HIV–related stigma scales, given that the degree of stigma is measured along a continuum, there is no clear prevalence cutoff for determining who is or is not "stigmatized". Although this was the first known use of the IARSS in India, questions with similar wording have been validated in India [28,32]. Further, we pilot–tested the questions on five Tamil and five Telugu speakers to ensure comprehensibility and face and content validity.

Sociodemographic variables of interest, collected as part of the standard YRG CARE patient questionnaire and clinical protocol, included gender, age, educational attainment, marital status (married vs other), employment status, rural/urban residence, language (Tamil/Telugu/other), sexual orientation ("homosexual," "heterosexual," or "bisexual"), alcohol use ("yes" vs "no" or "stopped"), and injection drug use (IDU) ("present use or previous use" vs "never use").

Statistical analysis

We used descriptive statistics to characterize the sample and to estimate the prevalence of probable depression, frequency of responses to the individual internalized stigma items, and mean PHQ–9 and IARSS scores. Responses were compared by gender using chi–square tests for categorical variables and t–tests for continuous variables. We then used Pearson correlation coefficient to estimate the correlation between internalized stigma (IARSS) and depressive symptoms (PHQ–9). We also dichotomized IARSS at the median value (0–2 vs 3–6) and compared probable depression by high and low internalized stigma score using a chi–square test.

Next, we used Poisson regression models [49,50], modified with robust estimates of variance [51,52], to estimate the association between probable depression and internalized stigma (IARSS score). Following Zou [49], the incidence rate ratios were interpreted as risk ratios. We estimated both unadjusted and adjusted models, with the latter including sociodemographic variables as potential confounders. A statistically significant regression coefficient for IARSS was considered evidence that an association existed between internalized stigma and probable depression. As an alternative parameterization, we fitted a multivariable linear regression model with depressive symptoms (PHQ–9 score) as the outcome of interest.

To explore the possibility of bias from unobserved confounders of the relationship between internalized stigma and depressive symptoms, we used the sensitivity analysis detailed in Oster [53]. This procedure assumes a value for the maximum R–squared from a regression model and calculates a value for the relative degree of confounding by unobserved vs observed variables (the "delta") that would result in a regression coefficient equal to zero. We selected a maximum R–squared value of 1.3 multiplied by the R–squared obtained in the multivariable linear regression model, as this is the level of robustness consistent with findings from randomized controlled trials [53].

RESULTS

524 persons entering into HIV care between January 2015 and May 2016 were enrolled into the study, including 304 men, 217 women, and 3 Hijra (transgender women). Because of the low number of Hijra

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Table 1. Characteristics of patients by gender

Characteristic	Overall (N = 521)	Women (N = 217)	Men (N = 304)	t–test / χ^2 statistic	P
Sociodemographic and clinical variables					
Age, mean (SD), y	39.6 (8.8)	37.1 (7.6)	41.3 (9.1)	5.50	<0.001*
Achieved more than primary education, %	63.7	56.7	68.8	7.98	0.005*
Married, %	67.0	53.5	76.6	30.8	<0.001*
Employed, %	75.6	45.2	97.4	187.2	<0.001*
Urban residence, %	35.3	33.6	36.5	0.46	0.50
Tamil speaker, %	19.6	17.1	21.4	1.51	0.22
Telugu speaker, %	76.4	81.6	72.7	5.52	0.02*
Heterosexual, %	96.4	98.6	94.7	5.43	0.02*
Baseline CD4+ cell count, mean (SD)	347.7 (493.3)	396.8 (345.7)	314.0 (571.1)	1.64	0.10
Substance use variables					
Current alcohol use, %	14.0	0	24.0	60.6	<0.001*
Injection drug use, %	0.4	0	0.7	1.43	0.23
Depressive symptoms and internalized stigma					
PHQ–9 score, mean (SD)	2.8 (3.3)	2.8 (3.2)	2.7 (3.4)	0.41	0.68
Probable depression, %	9.6	10.6	8.9	0.43	0.51
IARSS score, mean (SD)	2.4 (1.7)	2.3 (1.6)	2.5 (1.7)	1.46	0.15
It is difficult to tell people about my HIV infection, %	80.6	80.2	80.9	0.04	0.83
Being HIV positive makes me feel dirty, %	28.6	26.3	30.3	0.99	0.32
I feel guilty that I am HIV positive, %	26.3	24.4	27.6	0.67	0.41
I am ashamed that I am HIV positive, %	13.4	10.6	15.5	2.57	0.11
I sometimes feel worthless because I am HIV positive, %	15.6	12.0	18.1	3.60	0.06
I hide my HIV status from others, %	77.7	76.0	79.0	0.62	0.43

y – years, SD – standard deviation, PHQ–9 – Patient Health Questionnaire–9, IARSS – Internalized AIDS–Related Stigma Scale
*P<0.05.

enrolled, we dropped these three observations from the analyses. No one refused entry into the study, although not all eligible patients may have been approached because of variable interviewer availability. Participant characteristics are stratified by gender in **Table 1**. 502 (96%) self–reported as heterosexual. The mean age was 40 years (standard deviation (SD) 9 years). Prevalence of self–reported IDU was low (<1%). Telugu was the primary language of 76% of participants, with a majority of the remaining participants reporting Tamil as their primary language. The mean baseline CD4+ cell count (available for 394 participants) was 348 cells/mm³ (SD, 493).

The prevalence of probable depression was 10% and the mean PHQ–9 score was 2.8 (SD, 3.3). The scale reliability coefficient for the PHQ–9 was 0.80. The mean IARSS score was 2.4 (SD, 1.7). 427 (82%) participants endorsed at least one of the six IARSS items and 33 (6%) of participants endorsed all six IARSS items. The two IARSS items most commonly endorsed were related to concerns about disclosure: "I hide my HIV status from others" (78%) and "It is difficult to tell people about my HIV infection" (81%). The scale reliability coefficient for the IARSS was 0.79. The Pearson correlation coefficient between IARSS and the PHQ–9 was 0.47, indicating a correlation of moderate magnitude. 23% (44/192) of participants with an IARSS score of 3–6 screened positive for depression, compared to only 2% (6/329) of participants with an IARSS score of 0–2 ($\chi^2 = 62.2$, $P<0.001$).

In unadjusted analyses (**Table 2**), younger age, urban residence, being a Tamil speaker, current alcohol use, and higher IARSS score were associated with an increased risk of probable depression. After multivariable adjustment (**Table 2**), being a Tamil speaker and IARSS score were associated with increased risk of probable depression. The adjusted relative risk ratio for IARSS was 1.83 (95% confidence interval (CI) 1.56–2.14), indicating a nearly two times higher risk of screening positive for depression for each additional point on the IARSS. Turning next to the multivariable linear regression model with continuous depressive symptom severity (PHQ–9 score) as the outcome of interest, we observed a statistically significant positive association between IARSS and depressive symptoms (adjusted $b=0.91$; 95% CI 0.76–1.06). Put another way, we found an approximate increase in the PHQ–9 score of 0.9 for every additional point on the IARSS.

Table 2. Unadjusted and adjusted risk ratios and 95% confidence intervals for variables associated with probable depression

Variable	Unadjusted risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Female (vs other)	0.838 (0.494–1.422)	0.510 (0.248–1.051)
Age, per 10 year	0.725 (0.544–0.964)*	0.802 (0.619–1.037)
Achieved more than primary education (vs other)	1.012 (0.584–1.753)	1.094 (0.631–1.900)
Married (vs unmarried)	0.681 (0.400–1.158)	1.037 (0.604–1.780)
Employed (vs unemployed)	0.917 (0.503–1.672)	0.996 (0.511–1.942)
Urban residence (vs rural)	2.150 (1.270–3.641)*	1.298 (0.772–2.182)
Tamil speaker (vs other)	2.739 (1.623–4.621)**	1.986 (1.196–3.297)*
Current alcohol use	2.156 (1.205–3.859)*	1.807 (0.954–3.422)
IARSS score	1.907 (1.647–2.208)*	1.828 (1.559–2.143)**

CI – confidence interval, IARSS – Internalized AIDS–Related Stigma Scale
*P<0.05 and ** P<0.001.

In the sensitivity analysis exploring the robustness of the relationship between IARSS and depressive symptoms (PHQ–9 score), we assumed a maximum R–squared value of 0.267 (the R–squared obtained in the multivariable regression model) × 1.3 = 0.347, following the procedures described by Oster [53]. Using this maximum R–squared value, we calculated a delta of 2.34, indicating that confounding by unobserved variables would need to be more than twice as important as confounding by the observed variables in the regression model to generate a regression coefficient for IARSS equal to zero.

DISCUSSION

In this sample of newly diagnosed PLHIV entering into HIV care in southern India, we found a high prevalence of internalized stigma despite a relatively low prevalence of probable depression. The prevalence of probable depression in this study was 10%, which was lower than prior studies of Indian PLHIV [30,31,54]. The reasons for this lower prevalence of probable depression are unclear. One possible explanation may relate to a temporal trend in rising mean CD4+ cell count among patients presenting to YRG CARE, from approximately 160 in 2006 (unpublished data) to 347 in this cohort. In one study of Ugandan PLHIV from 2005–2012, there was a decline over time in mean depression symptom severity scores at ART initiation, a trend that appeared to be explained by improved physical health scores over time [55].

In contrast, we found that internalized stigma was reported commonly, with more than four–fifths of respondents endorsing at least one measure of internalized stigma. While relatively few respondents felt "guilty," "dirty," "ashamed," or "worthless" because of their serostatus, approximately four–fifths of respondents endorsed concerns about serostatus disclosure. This suggests that while most Indian PLHIV may not regard stigmatizing attitudes towards PLHIV as valid, they fear the consequences of disclosure and anticipate rejection and isolation from others [56]. This pattern is consistent with prior studies from India, which have found that PLHIV anticipate stigma much more frequently than they actually experience instances of enacted stigma [28]. Of note, while others have contended that the consequences of disclosure may be particularly harsh for Indian women with HIV, who may face financial hardship and rejection at the hands of husbands' families [57,58], we did not find significant gender differences in IARSS score or in responses to the items on serostatus disclosure. This contrasts with prior research with Indian PLHIV, which has found higher internalized stigma scores among men, primarily driven by gender differences in feelings of shame or guilt [27,33].

We also found that internalized stigma and depression were closely correlated. Nearly a quarter of participants with an IARSS score of 3–6, but only 2% with an IARSS score of 0–2, screened positive for depression. In a modified Poisson regression model adjusted for sociodemographic variables, we found that each additional point on the IARSS was associated with a nearly two times higher risk of probable depression. Our sensitivity analysis demonstrated that this finding was fairly robust, in that confounding by unobserved variables would need to be more than twice as important as confounding by observed variables to generate a regression coefficient for IARSS equal to zero. A person living with HIV who has internalized and accepted negative attitudes towards PLHIV as valid may suffer from self–hatred [59], hopelessness [60], isolation, and emotional distress [61]. Furthermore, a person living with HIV who harbors concerns about disclosure may lack social support and affirmation from family and friends. Fears of disclosure among Indian PLHIV have been linked to depressive symptoms [28] as well as poor outcomes such as failure to link to HIV care [9].

Further study is needed to determine whether depression and internalized stigma are associated with poor HIV treatment outcomes such as loss to care and lack of virologic suppression in India, and in particular whether the combination of depression and stigma is particularly deleterious. Such studies would highlight the importance of screening PLHIV for internalized stigma and depression at entry into care and ultimately reveal targets for policymakers to forestall loss from the HIV care continuum. For example, if fears of disclosure and the potential consequences of social rejection and economic incapacity are driving depressive symptoms and poor HIV–related outcomes, then interventions to help PLHIV safely disclose their serostatus or to bolster their economic capacity may help to keep PLHIV in care and on treatment.

There are several limitations to this study. First, as the study was conducted at a single HIV care center in India, the findings may not be generalizable to the entire country. In particular, given the high proportion of patients at YRG CARE who self–identify as heterosexual (although this number may be affected by disclosure bias), our findings may not be applicable to sexual and gender minorities. Nevertheless, we hope that our results will spur similar research among sexual and gender minorities and PLHIV who seek care in other parts of India and in the public sector. In addition, the type of private, multi–service program available at YRG CARE can be found in other cities in India as well as other Asian countries. Second, although the PHQ–9 can be used to identify persons with symptoms indicative of probable depression, we did not have access to data on DSM–consistent diagnoses of depressive disorders. However, the PHQ–9 has been shown to have good accuracy in diagnosing major depressive disorder in India [40,41]. Third, the IARSS, like other stigma scales, is limited by multiple factors, including 1) the difficulties inherent in operationalizing HIV–related stigma, a concept for which a consensus definition has been elusive [44,62], 2) the inability to draw conclusions on the "prevalence" of internalized stigma as no validated cut–off exists, and 3) the potential conceptual overlap between IARSS and other mental health measures such as the PHQ–9. While we acknowledge that the IARSS may not assess all aspects of internalized stigma among PLHIV and that we cannot comment on an exact "prevalence" of internalized stigma in our sample, our findings suggest an association between depression and the dimensions of internalized stigma in India captured by the IARSS–in particular, fears of serostatus disclosure and self–hatred. Finally, we encountered limitations in the use of the existing YRG CARE questionnaire for correlates of interest (in particular, the dichotomous nature of the alcohol use variable). Further research is needed to more precisely measure these variables, including measures of problem drinking, to understand possible associations with depression among Indian PLHIV.

In summary, we found that PLHIV entering into HIV care at a large ART center in southern India commonly endorsed fears of serostatus disclosure and that stigma and depression were closely correlated. Although there is likely a bidirectional relationship between stigma and depression among Indian PLHIV, as has been demonstrated in other LMICs [10,11], more study is needed to characterize the linkages between HIV–related stigma and depression in India specifically and the impact of these conditions on HIV–related outcomes. Depression and stigma may provide important targets for policymakers seeking to keep Indian PLHIV alive, in care, and on effective treatment.

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The effect of community health worker–led education on women's health and treatment–seeking: A cluster randomised trial and nested process evaluation in Gujarat, India

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Background A community–based health insurance scheme operated by the Self–Employed Women's Association in Gujarat, India reported that the leading reasons for inpatient hospitalisation claims by its members were diarrhoea, fever and hysterectomy – the latter at the average age of 37. This claims pattern raised concern regarding potentially unnecessary hospitalisation amongst low–income women.

Methods A cluster randomised trial and mixed methods process evaluation were designed to evaluate whether and how a community health worker–led education intervention amongst insured and uninsured adult women could reduce insurance claims, as well as hospitalisation and morbidity, related to diarrhoea, fever and hysterectomy. The 18–month intervention consisted of health workers providing preventive care information to women in a group setting in 14 randomly selected clusters, while health workers continued with regular activities in 14 comparison clusters. Claims data were collected from an administrative database, and four household surveys were conducted amongst a cohort of 1934 randomly selected adult women.

Results 30% of insured women and 18% of uninsured women reported attending sessions. There was no evidence of an intervention effect on the primary outcome, insurance claims (risk ratio (RR) = 1.03; 95% confidence interval (CI) 0.81, 1.30) or secondary outcomes amongst insured and uninsured women, hospitalisation (RR = 1.05; 95% CI 0.58, 1.90) and morbidity (RR = 1.09; 95% CI 0.87, 1.38) related to the three conditions. The process evaluation suggested that participants retained knowledge from the sessions, but barriers to behaviour change were not overcome.

Conclusions We detected no evidence of an effect of this health worker–led intervention to decrease claims, hospitalisation and morbidity related to diarrhoea, fever and hysterectomy. Strategies that capitalise on health workers' role in the community and knowledge, as well as those that address the social determinants of diarrhoea, fever and the frequency of hysterectomy – such as water and sanitation infrastructure and access to primary gynaecological care – emerged as areas to strengthen future interventions.

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Since the Alma–Ata declaration, community health workers (CHWs), also known as lay health workers, have been promoted as a key component of primary health care strategies aimed at women and children [1]. CHWs

have also been shown to be uniquely positioned to influence behavior change, through their use of indigenous knowledge and ability to communicate with empathy and locally appropriate language [2]. Evidence synthesised through meta–analyses, qualitative syntheses and disease–focused reviews thus far suggests that CHWs have the potential to improve knowledge, behaviour and health outcomes [3–8]. A 2010 Cochrane systematic review and meta–analysis of interventions involving lay health workers indicated moderate evidence of their potential to improve immunisation coverage, breastfeeding and adherence to tuberculosis treatment, primarily through one–to–one visits and linking women to health systems [4]. Evidence, albeit limited, also suggests that CHW–led education delivered to women in a group setting can improve knowledge and preventive behavior [9–16]. This paper reports on the findings of a cluster randomised trial and nested process evaluation of a CHW–led group health education intervention to improve women's health and treatment–seeking behaviour in a low–income setting in Gujarat, India.

Study setting

Gujarat, though one of India's wealthier states, performs close to national averages with regards to many health indicators. The last (2015–6) National Family Health Survey reported an infant mortality rate of 34/1000 live births and that only one–half (50.4%) of children between 12–23 months were fully immunised [17]. Utilisation of health services in Gujarat, as in most of India, is largely financed by individual households. Outpatient and inpatient care are predominantly sought in the private sector [18]. In 2009, Gujarat initiated roll–out of Rashtriya Swasthya Bima Yojana (RSBY), a government–financed health insurance scheme that provides hospitalisation coverage up to Rs 30 000 (US$ 442, 12.19.2016) for families identified to be below the poverty line [19]. In 2011, Gujarat recruited close to 30 000 village health workers (known as Accredited Social Health Activists, or ASHAs), one per 1000 population to cover its 18 539 villages [20].

The intervention was designed with the Self–Employed Women's Association (SEWA), a trade union of over 1.5 million women workers in India's informal economy, whose members typically have insecure employment and limited access to social protection. SEWA operates a community health worker–led health program and insurance scheme for its members, VimoSEWA, that provides up to Rs.5000 (74 USD, 19 December 2016) coverage for inpatient hospitalisation that exceeds 24 hours in exchange for annual premium payments by members.

Intervention

A 2009 analysis of 12 027 VimoSEWA hospitalisation claims reported that two of the leading reasons for inpatient hospitalisation amongst adult women were diarrhea and fever, the latter considered primarily related to malaria [21]. The third leading reason for insurance claims was hysterectomy, at a relatively low average age of 37. VimoSEWA was surprised by the high proportion of hospitalisation for diarrhoea and fever – seemingly common, preventable ailments. The frequency and age at hysterectomy suggested that some procedures may not have been medically indicated and were thus avoidable. Given that diarrhoea, fever and hysterectomy comprised over 40% of VimoSEWA's claims, SEWA aimed to design a scalable intervention to reduce claims, hospitalisation and morbidity related to the three conditions. If effective, the intervention would protect members from unnecessary hospitalisation as well as improve VimoSEWA's financial sustainability.

The aim of the intervention was to (i) raise awareness on prevention and immediate treatment for malaria–related fever and diarrhea and (ii) improve knowledge of hysterectomy and its side effects, in order to reduce medically unnecessary procedures. The intervention focused on group health education sessions implemented by its CHW team; this approach was viable with respect to the financial and human resources available. Operationally, SEWA defined health education as a tool to improve knowledge and change women's attitudes and behavior through information, dissemination and discussion. Further, since SEWA's CHWs were seasoned local leaders and activists, group education sessions could potentially engage women in community action. At the time of the intervention, SEWA CHWs conducted limited group health education programs, none of which addressed diarrhoea, fever/malaria or hysterectomy. Both intervention and control areas were exposed to information through government health programs, including ASHA home visits to mothers and children and limited media messaging. Messages included information on malaria and diarrhoea and did not address gynaecological ailments. However, since ASHAs were neither trained nor incentivised to conduct health education, SEWA felt a group–based intervention could fill an important gap in existing services. SEWA CHWs in intervention areas implemented three to five group health education sessions monthly with adult women over an 18–month period, while comparison area CHWs continued with regular activities (**Table 1**).

Table 1. CHW activities in comparison and intervention areas

ACTIVITY	INTERVENTION	COMPARISON
Home visits and group education on common illnesses (excluding diarrhoea, malaria and hysterectomy)	×	×
Accompanied referral to health services	×	×
Medicine sales and insurance promotion	×	×
Linkages with government providers	×	×
Activate Village Health and Sanitation Committees	×	×
Group education sessions on hysterectomy with film viewings	×	
Communication tools/handouts on hysterectomy	×	
Group education on diarrhoea with ORS demonstrations	×	
Group education on fever/malaria with interactive games	×	
Wall paintings on diarrhoea and malaria	×	
Education sessions on sanitation linkages and programs	×	
Monthly refresher training for CHWs	×	

ORS – oral rehydration salts, CHW – community health worker

METHODS

As the intervention was implemented at the CHW level, a cluster randomised trial was designed to evaluate the effect of the intervention on three outcomes: claims rates (primary outcome), hospitalisation and morbidity related to diarrhoea, fever and hysterectomy. Clusters were defined as the discrete geographical areas served by one CHW. The number of clusters included in the trial, 28 in total, was determined by the number of CHWs available in areas where VimoSEWA operates. The intervention was implemented in 14 randomly–selected CHW catchment areas of Ahmedabad city and rural areas of Ahmedabad district, with 14 comparison clusters. Randomisation was stratified by urban and rural location, as urban rates of claim submission had been observed to be higher than in rural areas in two previous studies at VimoSEWA [21,22]. Treatment allocation was assigned through randomly generated numbers and announced in a CHW meeting. Data collectors were not informed of cluster allocations.

Claims

Reduction in claims submission was measured by utilising all VimoSEWA insurance claims submitted in the intervention and control areas over the intervention period, as recorded in VimoSEWA's claims database. VimoSEWA considered the minimum worthwhile intervention effect to be a 30–40% reduction in claims for the three conditions. The cooperative had moved towards a sustainable model without external funding support; a smaller reduction in claims would not have justified funding a health intervention from its operational costs. The between–cluster coefficient of variation (k) was estimated to be 0.28 using data on claims submission rates in 2008–2009 [23]. The study was estimated to have 77% power ($P<0.05$, 2–sided test) to detect a 40% reduction in insurance claims for diarrhea, fever and hysterectomy.

Hospitalisation and morbidity

Data on hospitalisation and morbidity rates related to the three conditions were collected through household surveys. Both insured and uninsured women were included in the household survey to enable the investigation of predictors of insurance coverage and to investigate whether the effect of the intervention varied with insurance status. A sample size of 35 uninsured and 35 insured households per cluster was chosen – a total of 1960 households across 28 clusters. Household listings of insured women were provided by VimoSEWA. A listing of uninsured households was compiled by following CHWs on daily rounds. Households were randomly selected through computer generated numbering. A baseline survey was conducted from January to March 2010, followed by three survey rounds at six–month intervals following implementation of the intervention. An adult woman was selected for interview in each household: the same primary VimoSEWA policy holder or SEWA member in uninsured households was interviewed at each round. A total of 980 uninsured and 954 uninsured adult women were surveyed at baseline. Survey data were double–entered into a Microsoft Access database. A supervisor observed a random sub–set of interviews and checked each survey form manually before data entry. Attrition increased at each round, primarily due to demolition of slum pockets in Ahmedabad city and rural pre–monsoon seasonal migration: a total of 1616 households were surveyed in the final round (**Figure 1**).
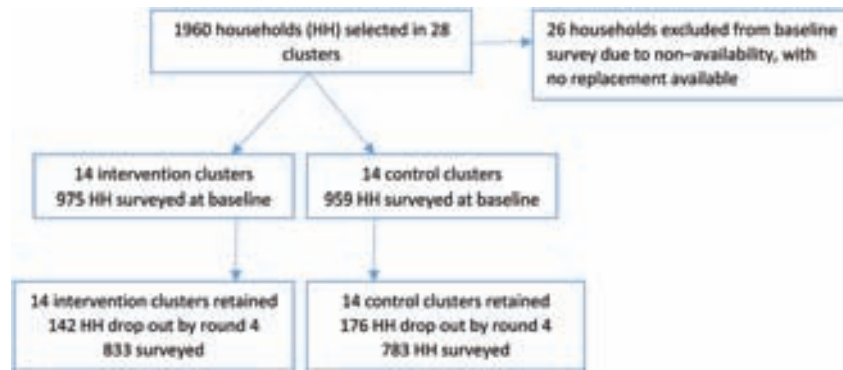
Figure 1. Cluster and survey participation.

Statistical methods

Analysis was by intention to treat. In the initial analysis, women's insurance status at baseline was used to define the insured and uninsured groups. A Poisson regression model with cluster–level random effects to account for between–cluster variation was fitted to estimate the effect of the intervention on claims rates for the three conditions [24]. Effect estimates were adjusted for rural–urban location and cluster–level baseline claims rates. Likelihood ratio tests comparing models with and without the intervention effect were performed to obtain p values. Analyses of the effect of the intervention on hospitalisation and morbidity rates for the three conditions were conducted using similar methods, adjusting for survey round, insurance status, rural/urban location and cluster–level baseline rates. Effect modification by rural/urban location was examined for all three outcomes and by insurance status for hospitalisation and morbidity. Lastly, a process evaluation collected quantitative and qualitative data at each step in the hypothesised causal chain (**Figure 2**).

Ethics and consent

Representatives of the clusters, drawn from SEWA's membership–based health cooperative, provided approval prior to randomisation. A board constituted by SEWA's Health Cooperative Executive Committee and the Ethics Committee of the London School of Hygiene and Tropical Medicine granted ethical approval for the intervention, evaluation and qualitative research. In light of low literacy levels in the study area, all households provided oral informed consent to participate in the survey, as approved by the local ethics board. The study was registered as ISRCTN21290274. Reporting follows the CONSORT guidelines and extension for cluster randomised trials.

RESULTS

Baseline comparability

Based on the demographic characteristics recorded in VimoSEWA's administrative databases, intervention and control arms were generally balanced, with the exception of differences in the proportions of agricul-
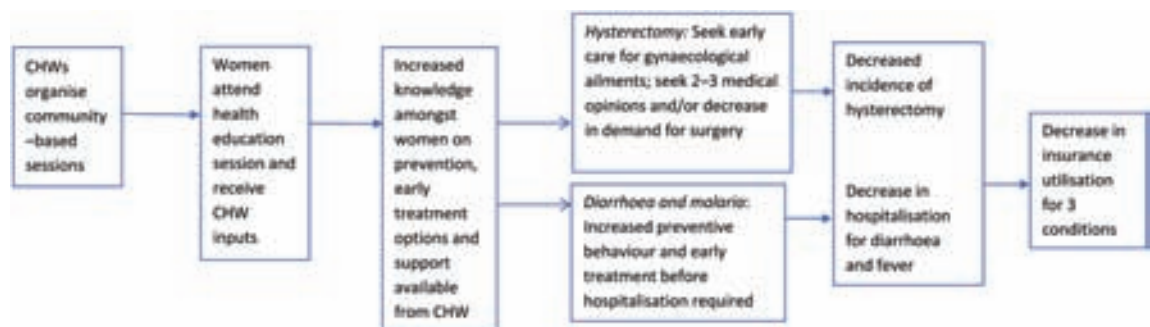
Figure 2. Intervention casual chain.

Table 2. Overview of baseline demographic characteristics, VimoSEWA membership database

	INTERVENTION (n = 1839)	COMPARISON (n = 1719)
Demographic variables:		
Mean age	37.7	37.1
% married	83.8	85.3
% widowed	10.1	9.4
Occupation:		
% agricultural	34.8	44.7
% service	37.3	36.5
% home–based	17.7	10.7
% unemployed	10.1	8.0
Baseline claims rate (/100 person–years)	5.7	5.0

tural and home–based workers (**Table 2**). Claims rates based on individual–level data and cluster summaries were similar (5.4 and 5.3 per 100 person–years). The between cluster coefficients of variation (k) in claims rates, estimated using baseline data, were 0.46 (urban) and 0.66 (rural).

Similarly, household survey data indicated that baseline demographic characteristics were largely balanced across intervention and comparison arms, including baseline rates of reported morbidity and hospitalisation (**Table 3**). However, latrine ownership was higher among intervention households than control households. Amongst insured women, a higher proportion had attended school and a higher proportion lived in a concrete home in the intervention arm. The between cluster coefficients of variation (k), estimated using baseline hospitalisation data, were 0.49 (urban) and 0.56 (rural). At baseline, the three focus conditions – fever/malaria, diarrheal illness and hysterectomy – comprised approximately half of all hospitalisations in the preceding 6 months amongst both insured and uninsured women (48 of 99 hospitalisations). Hysterectomy was the most common reason for hospitalisation. Hospitalisation rates among insured women were approximately double those among the uninsured.

Table 3. Baseline demographic characteristics, by insurance status and treatment arm

	UNINSURED (n = 980)		INSURED (n = 954)	
Selected variables	Intervention (n = 490)	Comparison (n = 490)	Intervention (n = 4698)	Comparison (n = 485)
Mean age in years	37.0	35.9	39.8	39.1
Mean household size	5.8	5.8	6.0	5.8
% concrete home	26.1	24.9	35.1	24.1
% with toilet	60.0	51.8	63.1	46.1
% individual drinking tap	76.7	75.5	76.7	73.3
Mean annual income (INR)	82 707	80 812	82 747	76 637
% never attended school	50.2	53.9	950.1	62.7
% respondents reported illness, past 30 d	13.5	12.0	15.9	19.2
% respondents reported hospitalization, past 6 mo	3.1	2.9	7.0	7.7

INR – Indian rupee

Table 4. Intervention outreach by insurance status (% women surveyed intervention areas, n = 833)

	MALARIA	DIARRHOEA	HYSTERECTOMY	ANY SESSION
Insured	23.2	25.0	13.2	30.3
Uninsured	13.6	14.1	6.3	18.2

Intervention coverage

In the end line survey, 30.3% of insured women and 18.2% of uninsured women in intervention clusters reported attending at least one session on diarrhoea, malaria or hysterectomy in the past year (**Table 4**). A lower proportion of women reported attending hysterectomy sessions compared to diarrhoea and malaria. Of 203 surveyed women who reported participating in a session, women who were insured, currently working and had attended at least primary school were more likely to attend.

Intervention effect on claims, hospitalisation and morbidity

During the 18–month intervention period, 3340 women residents in the study area were insured at some point, contributing 1436 person–years in the intervention arm and 1227 person–years in the comparison arm. These women submitted 140 claims for the three target conditions over the study period, with a slightly higher claims rate (5.5 per 100–person years) in the intervention arm, compared to 5.0 in comparison clusters. The estimated rate ratio, adjusted for location and cluster–level baseline claims rate was 1.03 (95% CI: 0.81–1.30, P = 0.81) (**Table 5**). There was no evidence that the effect of the intervention differed between rural and urban areas (P = 0.84).

The post–intervention hospitalisation rate for the three conditions was 2.7/100 person–years in the intervention arm, compared to 2.4/100 person–years in the comparison arm. After adjusting for insurance status, rural/urban location, survey round and baseline hospitalisation rates, there was no evidence of an intervention effect on hospitalisation rates for the three conditions (**Table 5**). There was no evidence of effect modification by insurance status ($P=0.91$) or by rural/urban location ($P=0.18$). Adjusting for imbalanced demographic characteristics identified at baseline and other potential covariates did not result in an important change in the point estimate or improve statistical efficiency (data not shown). Among initially insured women, hospitalisation rates decreased by approximately half in both intervention and control areas compared with pre–intervention rates, with smaller decreases observed among uninsured women (**Figure 3**).

Fever/malaria, diarrheal illness and gynaecological conditions comprised between 35–56% of reported morbidity in the past 30 days at baseline, with very few instances of gynaecological morbidity reported. The between cluster variation coefficients (k), calculated using baseline data, were 0.40 (urban) and 0.19 (rural). The post–intervention morbidity rate in the intervention area was 5.8/100 person–years, compared to 5.4/100 person–years in the control arm. There was no evidence of an intervention effect on morbidity for the three conditions (**Table 5**) or evidence of effect modification by insurance status ($P=0.75$) or rural/urban location ($P=0.37$).

Process findings

Observations of 20 education sessions noted two main findings regarding implementation quality: (i) a uniform, structured message was provided and reinforced by print media by most CHWs and (ii) communication abilities varied considerably. The majority (83%) of participants interviewed within a month

Table 5. Estimates of the effect of the intervention on claims, hospitalization and morbidity rates for three focus conditions using individual–level data, Poisson regression random effects model

	INTERVENTION (14 CLUSTERS)	COMPARISON (14 CLUSTERS)	EFFECT ESTIMATE	95% CI	P
Effect on claims*					
Claims for diarrhoea, fever, hysterectomy	79	61			
Total person–years	1756	1227			
Claims rate/100 person–years	5.50	5.04	1.03	0.81, 1.30	0.81
Effect on hospitalization rates†					
Total episodes of 3 conditions	36	31			
Total person–years	1355	1279			
Hospitalization rate/100 person–years	2.66	2.42	1.05	0.58, 1.90	0.88
Effect on morbidity rates†					
Total morbidity episodes, 3 conditions	157	140			
Total person–months	2705	2606			
Morbidity rate/100 person–months	5.80	5.37	1.09	0.87, 1.38	0.46

CI – confidence interval

*Adjusted for urban/rural location and cluster–level baseline claims rate.

†Adjusted for insurance status, location, survey round and cluster level baseline rate.
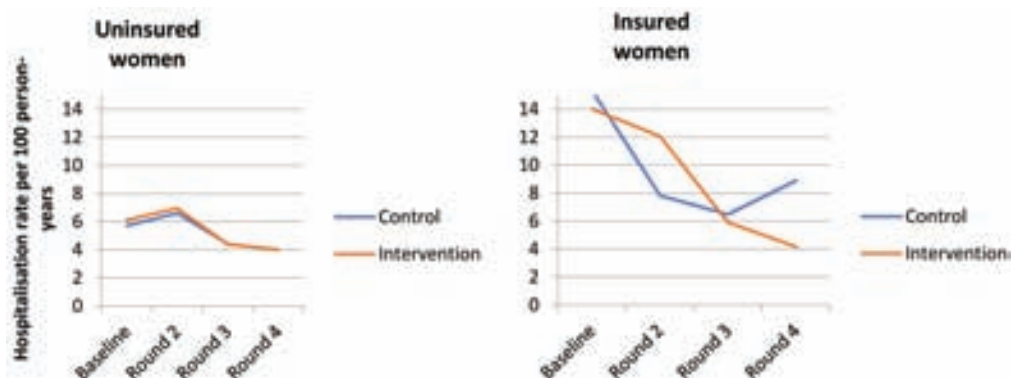
Figure 3. Hospitalisation rates by survey round, using insurance status at baseline.

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after attending an education session reported knowing how to control mosquitoes, while 45% reported knowing that handwashing with soap is an effective measure to prevent diarrhoea. Neither quantitative survey data nor qualitative interviews provided evidence of changes in behaviour related to handwashing or mosquito prevention, however. Health workers pointed to underlying determinants such as poor sanitation and lack of quality outpatient treatment as persistent barriers.

Regarding hysterectomy, 90% of women reported they would normally seek at least two opinions before undergoing hysterectomy. In–depth interviews with 10 participants suggested they gained: (i) increased knowledge and (ii) confidence in the local CHW as a resource person. However, understanding of potential side effects and the risk of premature menopause was low. Further, most women interviewed expressed that, despite learning new information, doctors' opinions would be the most important factor in a treatment decision. Interviews with CHWs and participants did not suggest a reduction in women's demand for hysterectomy, to the extent that such interviews could assess women's attitudes (**Figure 4**).

Figure 4. Summary of process findings for hysterectomy. Steps in causal pathway as defined in **Figure 2**.

DISCUSSION

In this setting, a high proportion of hospitalisations in adult women for diarrhoea, fever and hysterectomy was confirmed through both insurance claims and a household survey – indicating that the intervention targeted the conditions responsible for a major component of treatment sought by adult women in the study population. Although process findings suggested improvements in knowledge, we found no evidence of an effect of the intervention on care–seeking or health outcomes. These findings depart from several published studies that have reported evidence of an effect of CHW–led group health education on preventive health behaviours and some health outcomes related to malaria, family planning and women's health [9–16]. There are few published randomised trials, however, that do not report a positive effect of CHW–led group education on treatment–seeking or health outcomes, which may reflect both publication bias and, possibly, limited use of CHW–led group education as a strategy.

Three trials conducted in the United States of CHW–led group education sessions to improve screening rates for cervical and breast cancer amongst women in ethnic minority communities reported improved uptake of screening tests, two of which indicated that behaviour change was associated with improved knowledge. The third trial indicated that while group education improved breast cancer screening, it was more likely CHWs' social position and influence amongst women, rather than improved knowledge among the participants, that mediated behaviour change [15]. Non–randomised evaluations in India have reported increased health knowledge amongst women exposed to group education, with some evidence pointing to changes in treatment–seeking behaviour [25–27].

The trial evaluated an add–on education intervention in an ongoing CHW program that could have been easily scaled–up if found effective. The intervention delivery mechanism was aligned with two established characteristics of effective CHW programs: SEWA CHWs were embedded in their communities and were supported through continuous training and management inputs [5,28]. Intervention coverage was low, however. The intervention only included three sessions per month per CHW, because SEWA CHWs were already fully tasked with existing responsibilities and potentially overburdened – a common challenge to CHW programs that prevents greater coverage of interventions [5]. Nonetheless, CHW–led group education efforts in other settings suggested that even low numbers of meetings can trigger changes in behaviour [14,15]. In these cases, however, the intervention outcome was receipt of either a pap test or mammography– both one–time, preventive actions with logistical support by a CHW and readily available services.

Barriers from knowledge to behaviour change

Interventions that have demonstrated evidence of an effect on handwashing were considerably more intensive campaigns that included distribution of soap. A handwashing campaign in Karachi, Pakistan that included weekly education as well as soap distribution reported a sustained effect on handwashing with

soap, while a rural Indian education–only intervention did not detect evidence of improved behaviours [29–31]. Accordingly, SEWA's education sessions may not have been sufficiently intensive or targeted to trigger a change in preventive behaviour.

Regarding hysterectomy, qualitative research suggested that women who had undergone hysterectomy had previously suffered from untreated gynaecological morbidity such as excessive menstrual bleeding or fibroids that disturbed daily life and work [32]. Primary gynaecological care was not available, and providers typically suggested hysterectomy as a first- or second-line option for women who had completed childbearing. Lack of knowledge of side effects and sociocultural attitudes towards women's reproductive systems led providers and women to believe that the uterus was not a required organ once childbearing was complete. Most women were daily wage workers without any social protection; they explained that they chose to undergo the procedure to preserve their health and productivity. Although the intervention appeared to improve knowledge of hysterectomy and its side effects, it did not address these underlying health systems or sociocultural determinants.

Evaluation

This trial is that it was powered to detect a large (40%) reduction in claims for the three focus conditions. Though the data do not suggest any effect of the intervention on claims rates, the wide confidence intervals around the point estimates do not preclude the possibility of a smaller effect (<30%). VimoSEWA management had indicated that a reduction lower than 30–40% would not have significant financial bearing on the claims ratio, and would not be enough to justify funding an education intervention. The baseline survey reported a smaller number of hospitalisation events per cluster (and larger k) than initially assumed, suggesting that detecting this level of reduction was likely unrealistic. Lastly, 8% of women in control clusters also reported attending education sessions on the three conditions, which could reflect recall error or contamination – a further possible reason why the evaluation did not detect an intervention effect.

Given the observed coverage of the intervention – 30% of insured and 18% uninsured women in intervention areas reported attending sessions – the evaluation was not powered to detect the level of reduction in hysterectomy, diarrhoea and fever which might reasonably be expected. To illustrate in the case of hysterectomy, the most common reason for hospitalisation: assuming that the intervention effect was limited to the 10.5% of women who reported attending a hysterectomy session and that the intervention, if effective, would not have prevented more than 50% of hysterectomies among those women, there would have been, at most, a 5% reduction in an annual incidence of 21/1000 woman years (estimated from survey data) [33] – which corresponds to approximately three cases over the study period.

Strengths and limitations

The intervention outcomes – reported morbidity and hospitalisation rates and claims rates – were similar across arms at baseline for both insured and uninsured households, suggesting that randomisation achieved, in large part, its intended goal. We utilised claims data from the entire insured population, rather than a sample. In the survey, tracking both insured and uninsured women allowed the intervention to be examined from a community perspective, rather than solely for the insurance program. The claims data were not compromised by survey fatigue, attrition, recall errors or other limitations of self–reporting morbidity and hospitalisation that may have affected the household survey [34–39]. Lastly, the use of process and mixed methods data in addition to our randomised trial allowed us to examine its context, intended mechanisms and implementation gaps [28].

However, the decrease in self–reported hospitalisation in insured women not observed in the claims database suggests survey fatigue amongst respondents. The evaluation may have been improved by better accounting for attrition in the household survey. The initial estimate of 0.28 for k, considerably lower than that retrospectively calculated with baseline data, was based on aggregated rural and urban claims data, rather than manual categorisation into the three conditions as conducted during the trial analysis. Although the number of clusters was limited by the availability of CHWs, better estimation of between cluster–variation during the design phase would have made a stronger case to consider a larger sample size per cluster to improve power and precision, while noting the diminishing returns of increasing sample size given large values of k.

Regarding the intervention, our CHW–led education program may have been too ambitious in its intent to address three distinct ailments amongst both insured and uninsured women. Focusing on one condi-

tion may have allowed for wider coverage, stronger interventions and better implementation monitoring to alleviate concerns related to quality as well as contamination, although a larger number of clusters would have been required to evaluate the effect. Further, the use of formative research prior to the design might have provided important inputs on drivers of women's behaviour. For example, the hysterectomy component might have been strengthened by inclusion of an approach to provider behaviour or social norms.

Implications for CHW–led health education

Gaps in preventive knowledge suggest that health education remains a necessary, albeit not sufficient, intervention in this setting. Our findings also suggest that CHWs embedded in an on–going program may not be the most effective medium to disseminate information, in light of time constraints and variation in communication skills. Mobile technology could potentially standardise and support CHW–led health education efforts [40]. Mass media interventions are one alternative that does not depend on CHWs. Evaluations have reported moderate evidence for an effect of mass media on health behaviours when situated within multifaceted interventions [41]. Similarly, there is a moderate body of evidence that supports the effect of home visits by CHWs as a tool to change behaviour [3,42]. Although CHWs' existing responsibilities and SEWA's limited resources prevented a more intensive intervention, more structured individual follow–up and home visits could have potentially been included.

While women expressed trust in CHWs as sources of information and support in seeking treatment, our findings also suggest the need to reconsider a focus on individual behaviour change as the main goal of CHW–led health education. Earlier research conducted at SEWA suggested that women are hospitalised for diarrhoea and fever after outpatient treatment repeatedly failed [43], while hysterectomy emerged as a symptom of weak health services and embedded social norms. Thus, even with improved coverage and quality of a health education intervention, an approach premised on changing individual knowledge and action alone may have been insufficient to affect health outcomes. Instead, CHW–led interventions could have utilised group education processes to instigate collective action for improved water and sanitation, for example. Similarly, an advocacy component led by CHWs to address the drivers of hysterectomy, such as the lack of gynaecological care in primary health care settings, could have been explored. CHWs' position as bearers of both technical knowledge and indigenous experience could have been better capitalised upon, through their roles as educator–advocates in the community.

CONCLUSION

The high proportion of insurance claims utilised for seemingly preventable illnesses emphasises the need for design and evaluation of scalable, community–based strategies to address common causes of hospitalisation amongst low–income women. The wide coverage and reach of CHWs in India, particularly government ASHAs, is a potential opportunity to reach women with preventive health interventions. Our evaluation suggests that, while CHW–led health education was not sufficient to reduce hospitalisation, strategies that capitalise upon CHW strengths – their position in the community, practical skills and local knowledge – should continue to be experimented with for their potential to strengthen health systems and improve women's health outcomes.

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PAPERS

Strategies for prevention of gastrointestinal cancers in developing countries: a systematic review

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Background Gastrointestinal cancers account for one third of total cancer incidence and mortality in developing countries. To date, there is no systematic synthesis of evidence regarding strategies to prevent gastrointestinal cancers in developing countries. We aimed to provide a systematic overview of studies evaluating strategies for prevention or early detection of the three most common gastrointestinal cancers (gastric, liver and colorectal cancer) in developing countries.

Methods We searched MEDLINE, Web of Science and WHO Global Index Medicus databases for relevant articles published until October 2016 using combinations of the search terms "gastrointestinal", "digestive system", "gastric", "liver", "colorectal", "cancer", "prevention", "early detection" and "developing country" (including names).

Results Overall, 73 articles met the inclusion criteria, providing information on short– and long–term outcomes (up to 30 years) from various intervention studies (~45% randomized). Trials on hepatitis B vaccination consistently showed vaccine efficacy over time and indicated long–term preventive effects on liver cancer incidence that start to become measurable at the population level. Studies on anti–*H. pylori* treatment suggested a reduction in gastric cancer incidence reaching statistical significance after long–term follow–up, while evidence regarding a preventive effect in persons with precancerous lesions is still inconclusive. The studies regarding colorectal cancer focused on early detection, ~90% of which were restricted to intermediate endpoints.

Conclusion In conclusion, there were a number of studies on gastric and liver cancer prevention in developing countries showing promising results after long–term follow–up. Important next steps include pooled meta–analyses as far as possible given the heterogeneity between studies as well as implementation research.

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Cancer is a leading health burden and cause of death worldwide, with approximately 14 million new cases and 8 million deaths per year globally [1]. Despite the general understanding that cancer is primarily a problem of the (industrially) developed world, more than 60% of cancer cases and 70% of cancer deaths were estimated to occur in developing countries in 2008 [2]. Gastrointestinal cancers (GICs) are estimated to account for one third of total cancer incidence and mortality in developing countries [1]. With almost 2 million new cases and 1.5 million deaths in 2012, gastric, liver and colorectal cancers (CRC) are currently estimated to be the three most common GICs in the less developed regions of the world, where they account for 24%, 23% and 22% of all GICs, respectively [1].

Despite extensive efforts to improve treatment of metastatic disease including the development of new drugs, the prognosis for advanced stages of gastric, liver and colorectal cancer remains poor even in developed countries, with 5–year relative survival rates (regional and distant stages combined) of 33%, 8% and 49% in the US in 2016, respectively [3]. These figures highlight the need for further efforts to realize the high potential of primary prevention and early detection of these GICs. This is particularly relevant for developing countries where up–to–date treatment of advanced stage cancers may additionally be limited due to infrastructure and economic constraints.

To date there has been no systematic review regarding strategies to prevent these GICs in developing countries. We therefore aimed to conduct a systematic literature search and provide an overview of studies evaluating strategies for prevention or early detection of the three most common gastrointestinal cancers (gastric, liver and colorectal cancer) in developing countries.

METHODS

Search strategy

We searched MEDLINE, Web of Science and WHO Global Index Medicus databases for articles published until October 2016. We used a comprehensive search strategy with no restriction regarding publication date, type of participants (eg, age or sex characteristics), type of interventions, study design or type of outcome measures. A detailed description of our search strategy is provided in Appendix S1 in **Online supplementary document**. In brief, we used both free text keywords and for the MEDLINE search also MeSH (Medical Subject Heading) terms. Regarding the latter, we used the MeSH terms gastrointestinal cancer, digestive system cancer (entailing gastric, colorectal and liver cancer as MeSH sub–categories), prevention, early detection of cancer, and developing country, as search terms.

We used the United Nations Development Programme (UNDP) country classification (for the year 2013), which utilizes Human Development Index (HDI) as basis of country groupings, for determining countries with "developing" status. The classification groups all countries in very high, high, medium and low HDI clusters. Countries with high, medium and low HDI are classified as developing countries. Consequently, the names of 140 developing countries were also used as search terms. The names of these countries are listed in Appendix S2 in **Online Supplementary Document**. In addition to the database searches, we employed cross–referencing to complement the study identification process. Duplicate publications were deleted. In a first step, each title and abstract was screened, to determine whether the article was potentially relevant for the review topic. In a next step, the full text of potentially relevant articles was reviewed to assess whether inclusion criteria were fulfilled. This was done independently by both authors.

Inclusion and exclusion criteria

We included studies that aimed at evaluating strategies for prevention of gastric, liver and colorectal cancer in developing countries. We only included studies on humans published in English. We focused on studies that reported disease–related outcomes such as long–term health outcomes (eg, reduction of incidence or mortality) or intermediate outcomes that are expected to be associated with long–term effects (eg, detection rates or vaccine efficacy). Accordingly, we excluded non–original articles (eg, case reports, commentaries, guidelines etc.) and studies that were restricted to health behavior.

Data extraction

All studies meeting the inclusion criteria were categorized by cancer type (gastric cancer, liver cancer, colorectal cancer). Within these categories, we ordered the studies by the type of intervention or preventive strategy. We extracted the following information in a standardized manner from all included studies: author, publication year, preventive measure including details such as the intensity and length of interventions or the number of screening rounds, country and region within the country, study design, study population (sample size, sex distribution and age), outcomes under study and results. If the same study population was examined at different time points after the intervention, we extracted the information on the outcomes under study and results for each follow–up. Both authors reviewed the articles independently and any disagreement was resolved by consensus.

We applied the Preferred Reporting Items for Systematic Reviews and Meta–Analyses (PRISMA) guidelines criteria as far as it was possible, given the heterogeneity of the studies. The PRISMA Checklist is provided in Appendix S3 in **Online Supplementary Document**.

RESULTS

Overall, our initial search yielded 7315 entries. After deleting duplicates (n = 765) and excluding articles that were not relevant to the topic according to their title and abstract (n = 6467), 83 articles were selected for the full text review. Of these, 55 articles were relevant. Another 18 relevant articles were identified by cross–referencing, yielding in total 73 articles (**Figure 1**). The underlying number of studies is lower (n = 54) because several articles refer to the same study but report on different follow–up periods or outcomes.

Gastric cancer

Studies on gastric cancer prevention could be classified into three main categories: supplementation with vitamins and minerals (4 randomized trials), anti–*H. pylori* treatment (12 randomized trials) and early detection with an occult blood bead detector, with photofluorography, with X–ray or direct gastroscopy (5 cross–sectional diagnostic studies, 2 case–control studies and 1 non–randomized intervention trial). **Table 1** provides detailed information about these studies [4–34].

Studies on vitamin and mineral supplementation (eg, vitamin A, B vitamins, selenium etc.) considered reduction in gastric cancer incidence and mortality [4,6,7,9,10] or changes regarding precancerous lesions as outcomes [5,8,11]. All these studies were conducted in China except one [11]. The duration of supplementations ranged between 2–6 years and follow–up periods between 5 and 26 years.

The supplementation of a combination of beta–carotene, vitamin E and selenium showed a (marginally) statistically significant reduction in gastric cancer mortality of 20% (relative risk (RR) = 0.79, 95% confidence interval (CI) 0.64–0.99) [4]. Other studies, partly conducted in high–risk subjects did not show statistically significant effects [5–11].

Studies on anti–*H. pylori* treatment considered reduction in gastric cancer incidence and mortality [15,17,20,21] or other outcomes eg, changes regarding precancerous lesions or *H. pylori* cure rate [12–14,16,18,19,22–26]. Eleven studies were conducted in China [13–17,19–22,24,26] and four studies in
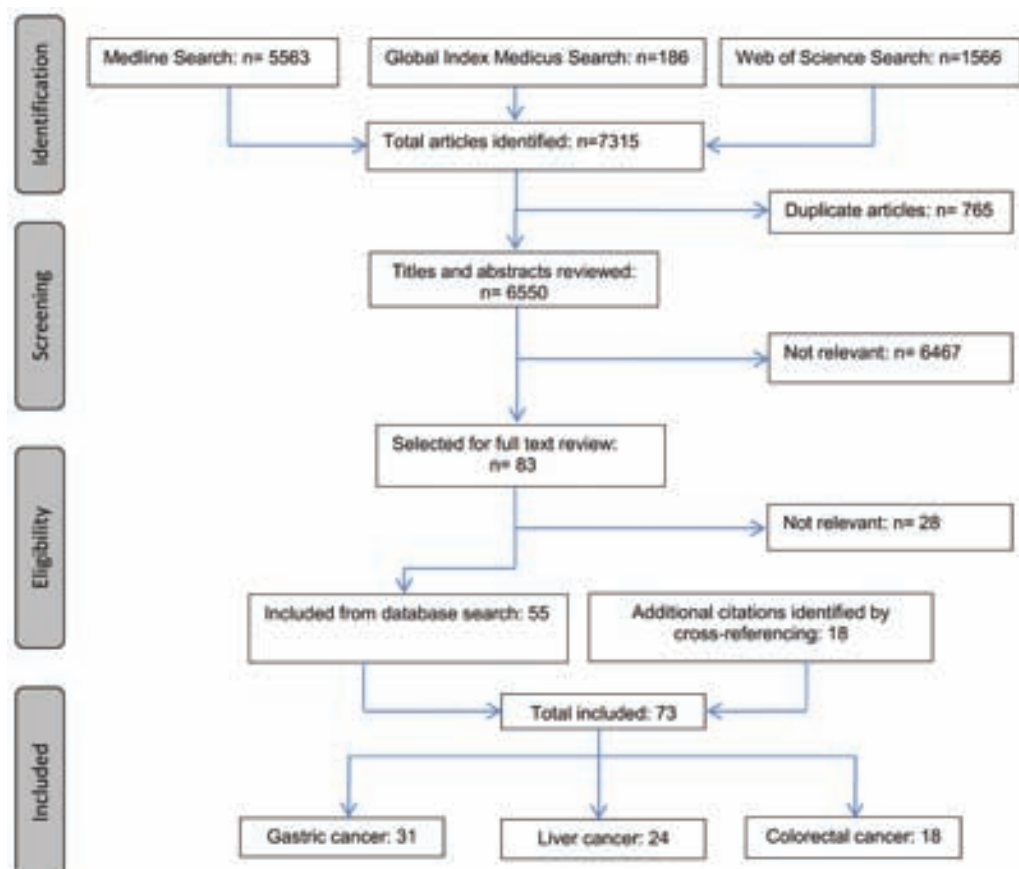
Figure 1. Flow diagram of the literature search process.

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Table 1. Studies investigating strategies for prevention of gastric cancer

Author(s), year	Preventive measure/screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results	
Supplementation with vitamins and minerals							
Blot et al., 1993 [4]; Wang et al., 1994 [5]; Qiao et al., 2009 [6]	Daily supplementation of: Factor A (retinol+zinc); Factor B (riboflavin+niacin); Factor C (vitamin C+molybdenum); Factor D (beta–carotene+vitamin E+selenium); Duration of supplementation: 5.25 y	China (Linxian)	Randomized trial with 2^4 factorial design	Sample size: n=29 584; Sex distribution: 45% male; Age: range: 40–69 y	RR regarding reduction of gastric cancer incidence and mortality determined at the end of the intervention period; OR regarding reduction of prevalence of gastric dysplasia and cancer determined by endoscopic evaluation at the end of the intervention period; HR regarding reduction of gastric cancer mortality determined at 15 y follow–up	**RR regarding gastric cancer incidence:** Factor A: 0.96 (95% CI 0.81–1.14) Factor B: 1.04 (95% CI 0.88–1.23) Factor C: 1.10 (95% CI 0.92–1.30) Factor D: 0.84 (95% CI 0.71–1.00) **OR regarding dysplasia or cancer:** Factor A: 0.58 (95% CI 0.24–1.39) Factor B: 1.32 (95% CI 0.56–3.14) Factor C: 2.64 (95% CI 1.01–6.93) Factor D: 0.83 (95% CI 0.35–2.01) **HR regarding gastric cancer mortality:** Factor A: 0.97 (95% CI 0.87–1.09) Factor B: 0.90 (95% CI 0.88–1.10) Factor C: 1.05 (95% CI 0.94–1.18) Factor D: 0.89 (95% CI 0.79–1.00)	**RR regarding gastric cancer mortality:** Factor A: 1.03 (95% CI 0.83–1.28) Factor B: 1.00 (95% CI 0.81–1.24) Factor C: 1.09 (95% CI 0.88–1.36) Factor D: 0.79 (95% CI 0.64–0.99) **OR regarding gastric cancer:** Factor A: 0.38 (95% CI 0.13–1.15) Factor B: 1.67 (95% CI 0.58–4.76) Factor C: 2.75 (95% CI 0.86–8.84) Factor D: 1.05 (95% CI 0.37–2.92)
Li et al., 1993 [7], Dawsey et al., 1994 [8], Wang et al., 2013 [9]	Daily supplementation of: 14 vitamins and 12 minerals; Duration of supplementation: 6 y	China (Linxian)	Randomized two–armed placebo–controlled trial	Sample size: n=3318 (adults with cytologically detected oesophageal dysplasia); Sex distribution: 44% male; Age: median: 54 y	RR regarding reduction of gastric cancer incidence and mortality; OR regarding reduction in the prevalence of gastric dysplasia and cancer determined by endoscopic evaluation at 2.5 and 6 y follow–up; HR regarding reduction of gastric cancer mortality determined at 26 y follow–up	**RR regarding gastric cancer incidence:** 1.17 (95% CI 0.87–1.58) **Lesion prevalence at 2.5 y:** Dysplasia or cancer: OR: 2.49 (95% CI 0.94–6.58) Gastric cancer: OR: 1.91 (95% CI 0.64–5.68) **HR regarding gastric cancer mortality:** 0.91 (95% CI 0.73–1.13)	**RR regarding gastric cancer mortality:** 1.18 (95% CI 0.76–1.85) **Lesion prevalence at 6 y:** Dysplasia or cancer: OR: 0.77 (95% CI 0.41–1.47) Gastric cancer: OR: 0.77 (95% CI 0.38–1.58)
Li et al., 2004 [10]	Supplementation of: allitridum (daily) and selenium (every other day); Duration of supplementation: 2 months supplementation in 2 y	China (Shandong)	Randomized two–armed placebo–controlled trial	Sample size: n=5033; Sex distribution: 65% male; Age: range: 35–74 y	RR regarding gastric cancer determined at 5 y follow–up	RR: 0.48 (95% CI 0.21–1.06) Subgroup analysis restricted to males: RR: 0.36 (95% CI 0.14–0.92)	
Plummer et al., 2007 [11]	Daily supplementation of: vitamin C, vitamin E and beta carotene; Duration of supplementation: 3 y	Venezuela (Tashira)	Randomized two–armed placebo–controlled trial	Sample size: n=1980; Sex distribution: 47% male; Age: range: 35–69 y	RR regarding regression of precancerous lesions	RR:1.02 (95% CI 0.90–1.33)	

Table 1. Continued

Anti *H. pylori* treatment

Author(s), year	Preventive measure/screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results
Correa et al., 2000 [12]	Anti-*H. pylori* treatment with: amoxicillin, metronidazole and bismuth subsalicylate; Duration of treatment: 2 weeks; Daily supplementation of: beta–carotene and/or ascorbic acid; Duration of supplementation: 6 y	Colombia (Nariño)	Randomized placebo–controlled trial with 2³ factorial design	Sample size: n=852 (individuals with precancerous lesions – multi–focal atrophy and/or intestinal metaplasia); Sex distribution: 46% male; Age: mean: 51 y	RR regarding regression of precancerous lesions at 7 y follow–up	**Multi–focal atrophy:** Anti-*H. pylori* treatment: RR: 4.80 (95% CI 1.60–14.20) Beta–carotene: RR: 5.1 (95% CI 1.70–15.00) Ascorbic acid: RR: 5.00 (95% CI 1.70–14.40) **Intestinal metaplasia:** Anti-*H. pylori* treatment: RR: 3.10 (95% CI 1.00–9.30) Beta–carotene: RR: 3.40 (95% CI 1.10–9.80) Ascorbic acid: RR: 3.30 (95% CI 1.10–9.50)
Sung et al., 2000 [13]; Zhou et al., 2014 [14]	Anti-*H. pylori* treatment with: omeprazole, amoxicillin and clarithromycin; Duration of treatment: 1 week	China (Yanati)	Randomized two–armed placebo–controlled trial	Sample size: n=587 (*H. pylori* positive); Sex distribution: 50% male (treatment group), 46% male (placebo group); Age: mean: 50 y (treatment group), 51 y (placebo group)	Changes in histologic grading: determined at 1 y follow–up; determined at 10 y follow–up	Regression of gastric atrophy: (P=0.94) Regression of intestinal metaplasia: (P=0.52) **Regression of gastric atrophy:** RR: 0.88 (95% CI 0.79–0.97) in antrum RR: 0.62 (95% CI 0.49–0.77) in corpus **Regression of intestinal metaplasia:** RR: 0.85 (95% CI 0.78–0.92) in antrum RR: 0.87 (95% CI 0.74–1.02) in corpus **Regression of atypical dysplasia:** RR: 1.33 (95% CI 0.85–2.07) in antrum RR: 1.01 (95% CI 0.38–2.68) in corpus
Guo et al., 2003 [15]	Health education: both intervention and control group; Treatment of high risk subjects (with precancerous lesions): antibiotics, Chinese herb medicine and nutritional therapy (only intervention group)	China (Zhuanghe)	Cluster–randomized two–armed controlled intervention study	Sample size: n=100966 (of which n=1781 were identified as high risk subjects); Sex distribution: 51% male (intervention group), 50% male (control group); Age: >35 y	RR regarding gastric cancer mortality at 3 y follow–up	RR: 0.50 (95% CI 0.34–0.73)
Zhou et al., 2003 [16]	Anti-*H. pylori* treatment with: omeprazole, clarithromycin and amoxicillin; Duration of treatment: 1 week	China (Shandong)	Randomized two–armed placebo–controlled trial	Sample size: n=552 (*H. pylori* positive); Sex distribution: n.r.; Age: range: 35–75 y	Proportion of subjects in whom severity of precancerous lesions has improved/not changed since baseline in *H. pylori*–positive vs *H. pylori* negative subjects at 5 y follow–up	Only for intestinal metaplasia in antrum the proportion of subjects in whom lesion severity has improved/not changed was higher in *H. pylori* negative vs *H. pylori* positive subjects: 71% vs 61% (P=0.032). For other lesions in the antrum and for lesions in the body there were no significant differences in the proportions.

Table 1. Continued

Author(s), year	Preventive measure/screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results
Wong et al., 2004 [17]	Anti–H. pylori treatment with: omeprazole, amoxicillin, clavulanate potassium and metronidazole; Duration of treatment: 2 weeks	China (Fujian)	Randomized two–armed placebo–controlled trial	Sample size: n=1630 (healthy carriers of H. pylori); Sex distribution: 54% male; Age: mean: 42 y	HR regarding gastric cancer incidence at 7.5 y follow–up; Subgroup analysis restricted to subjects without precancerous lesions	HR: 0.63 (95% CI 0.24–1.62) n=0 in treatment group vs n=6 in control group (P=0.02)
Ley et al., 2004 [18]	Anti–H. pylori treatment with: omeprazole, amoxicillin and clarithromycin; Duration of treatment: 1 week	Mexico (Chiapas)	Randomized two–armed placebo–controlled trial	Sample size: n=248 (healthy carriers of H. pylori); Sex distribution: 37% male; Age: mean: 51 y (treatment group), 52 y (control group)	H. pylori cure rate at 6 weeks and 1 y follow–up; Changes in worst biopsy diagnosis at 6 weeks and 1 y follow–up	Cure rate: 6 weeks: 79% (treatment) vs 3% (placebo) (P<0.001) 1 y: 76% (treatment) vs 2% (placebo) (P<0.001) No difference regarding the change in worst biopsy diagnosis between groups.
You et al., 2006 [19]; Ma et al., 2012 [20], Li et al., 2014 [21]	Anti–H. pylori treatment / supplementation in H. pylori seropositives with: omeprazole, amoxicillin and/or garlic supplements and/or vitamins/minerals (vitamin C, vitamin E and selenium); Duration of treatment: 2 weeks; Supplementation in H. pylori seronegatives with: garlic and/or vitamin C, vitamin E and selenium; Duration of supplementation: 7.3 y	China (Shandong)	Randomized placebo–controlled trial with 2^3 and 2^2 factorial design	Sample size: n=3365; H. pylori seropositives: n=2258; H. pylori seronegatives: n=1107 (all underwent gastroscopy at baseline); Sex distribution: 51% male; Age: mean: 47 y; range: 35–64 y	OR regarding reduction in the prevalence of advanced precancerous lesions determined at 3.5 and 7.5 y follow–up; OR regarding gastric cancer incidence and HR regarding gastric cancer mortality determined at 15 y follow–up; Subgroup analysis in subjects ≥55 y (results refer to anti–H. pylori treatment).	**Prevalence of advanced precancerous lesions:** Anti–H. pylori treatment: 3.5 y: OR=0.77 (95% CI 0.62–0.95) 7.5 y: OR=0.60 (95% CI 0.47–0.75) Garlic: 3.5 y: OR=0.9 (95% CI 0.84–1.18) 7.5 y: OR=1.08 (95% CI 0.90–1.29) Vitamins/minerals: 3.5 y: OR=1.32 (95% CI 1.12–1.57) 7.5 y: OR=1.14 (95% CI 0.96–1.37) **Gastric cancer incidence / Gastric cancer mortality** Anti–H. pylori treatment: OR: 0.61 (95% CI 0.38–0.96) / HR: 0.67 (95% CI 0.36–1.28) Garlic: OR: 0.80 (95% CI 0.53–1.20) / HR: 0.65 (95% CI 0.35–1.20) Vitamins/minerals: OR: 0.81 (95% CI 0.54–1.22) / HR: 0.55 (95% CI 0.29–1.03) **Gastric cancer incidence / Gastric cancer mortality** OR: 0.36 (95% CI 0.17–0.79) / HR: 0.26 (95% CI 0.09–0.79) **Gastric cancer incidence among subjects with intestinal metaplasia and dysplasia:** OR: 0.56 (95% CI 0.34–0.91)
Ji et al., 2006 [22]	Anti–H. pylori treatment with: omeprazole/ lansoprazole, clarithromycin, bismuth citrate and tinidazole; Duration of treatment: 2 weeks	China (Zhejiang)	Randomized two–armed placebo–controlled trial	Sample size: n=48 (with hyperplastic gastric polyps and H. pylori+); Sex distribution: 54% male; Age: range: 21–73 y; mean: 49 y (treatment arm), 47 y (control arm)	H. pylori cure rate; Polyp disappearance rate determined at 1 y follow–up	Treatment arm: 86% (95% CI 63%–99%); Control arm: 0% (95% CI 0%–21%) Treatment arm: 68% (95% CI 54%–91%); Control arm: 0% (95% CI 0%–21%)

Table 1. Continued

Author(s), year	Preventive measure/screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results
Sari et al., 2008 [23]	Anti–H. pylori treatment with: clarithromycin, amoxicillin and proton pump inhibitor; Duration of treatment: 2 weeks	Turkey	Randomized two–armed intervention study	Sample size: Group 1: n=70 (H. pylori⁺ index patients and their H. pylori⁺family members); Group 2: n=70 (only H. pylori⁺index patients treated); Sex distribution: n.r.; Age: mean: 42 y	Rate of H. pylori positives determined at 9 month follow–up	Group 1: 7%; Group 2: 39%; OR: 8.61 (95% CI 2.91–22.84)
Wong et al., 2012 [24]	Anti–H. pylori treatment with: omeprazole, amoxicillin and clarithromycin followed by celecoxib; Duration of treatment: Anti–H. pylori: 1 week; Celecoxib: 2 y	China (Linqu)	Randomized placebo–controlled trial with 2² factorial design	Sample size: n=1024 (H. pylori⁺ patients with advanced PLs); Sex distribution: 46% male; Age: range: 35–64 y	OR regarding regression of advanced PLs determined at 2 y follow–up	**Regression of advanced PLs:** Anti–H. pylori treatment: OR: 1.80 (P=0.009); Celecoxib: OR: 1.55 (P=0.04); Anti–H. pylori treatment+celecoxib: OR: 1.50 (P=0.067)
Massarrat et al., 2012 [25]	Anti–H. pylori treatment with: bismuth subcitrate, metronidazole and furazolidone; Duration of treatment: 2 weeks	Iran (Tehran)	Randomized two–armed placebo–controlled trial	Sample size: n=521 (H. pylori⁺ 1st degree relatives of gastric cancer patients); Sex distribution: 49% male; Age: mean: 48 y; range: 38–70 y	Proportion of subjects in whom severity of PLs changed by at least one score in the treatment group vs the control group determined at 2.5 and 4.5 y follow–up	**Atrophy in antrum:** 2.5 y: 62% vs 31% (P<0.0001) 4.5 y: 50% vs 30% (P>0.05) **Atrophy in corpus:** 2.5 y: 36% vs 13% (P<0.001) 4.5 y: 43% vs 21% (P<0.02) **Intestinal metaplasia in antrum:** 2.5 y: 35% vs 28% (P>0.05) 4.5 y: 38% vs 21% (P>0.05) **Intestinal metaplasia in corpus:** 2.5 y: 9% vs 10% (P>0.05) 4.5 y: 20% vs 29% (P>0.05)
Pan et al., 2016 [26]	Anti–H. pylori treatment with: high dose of tetracycline, metronidazole, omeprazole and bismuth citrate (group 1) or placebos of tetracycline and metronidazole plus low dose of omeprazole and bismuth citrate (group 2)	China (Linqu)	Cluster–randomized two–armed placebo–controlled trial	Sample size: group 1: n=44345; group 2: n=43930 (all H. pylori positive); Sex distribution: 42% male; Age: range: 25–54 y; median:43 y	H. pylori cure rate assessed 45 days after treatment	Group 1: 73%; Group 2: 15%
Early detection						
Qin et al., 1988 [27]	Occult blood bead detector; positive results followed up by gastroscopy	China (Henan & Jiangsu)	Cross–sectional diagnostic study	Sample size: n=38073; Sex distribution: 42% male; Age: range: 35–70 y	Positivity rate; Gastric cancer detection rate; Proportion of gastric cancers detected at an early stage	24% (9204/38073); 0.2% regarding the whole study population (85/38073); 2% regarding those who underwent gastroscopy (85/4023); 45% (57/126)

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Table 1. Continued

Author(s), year	Preventive measure/screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results
Qin et al., 1997 [28]	Occult blood bead detector; positive results followed up by gastroscopy	China (Henan)	Cross-sectional diagnostic study	Sample size: n=4970; Sex distribution: n.r.; Age: range: 30–70 y	Positivity rate; Gastric cancer detection rate; Proportion of gastric cancers detected at an early stage	7% (372/4,970); 0.2% regarding the whole study population (11/4,970); 1% regarding those who underwent gastroscopy (11/817); 84% (9/11)
Pisani et al., 1994 [29]	Photofluorography	Venezuela (Tashira)	Case–control study	Sample size:n=241 (cases), n=2410 (controls); Sex distribution: n.r.; Age: ≥35 y	OR regarding reduction in gastric cancer mortality	OR: 1.26 (95% CI 0.83–1.91)
Rosero–Bixby et al., 2007 [30]	X-ray	Costa Rica (Cartago and Perez Zeledon)	Non-randomized community–controlled study (measures before and after intervention)	Sample size: n=6828; Sex distribution: 64% male; Age: mean: 64 y	Gastric cancer death rate at 2–7 y follow-up in the intervention group vs four control groups	Reduction in death rate by 48–59% (P<0.05)
Zhang et al., 2002 [31]	Direct gastroscopy	China	Cross-sectional diagnostic study	Sample size: n=3048; Sex distribution: 95% male; Age: range 60–93 y; mean: 70 y	Gastric cancer detection rate; Proportion of gastric cancers detected at an early stage	3% (92/3048); 63% (58/92)
Lu et al., 2014 [32]	Direct gastroscopy	China (Henan)	Cross-sectional diagnostic study	Sample size: n=36154; Sex distribution: 59% male; Age: range 40–69 y	Gastric cancer detection rate; Proportion of gastric cancers detected at an early stage	0.84% (307/36154); 79% (243/307)
Zheng et al., 2015 [33]	Direct gastroscopy	China (Yangzhong)	Cross-sectional diagnostic study	Sample size: n=12453; Sex distribution: 43% male; Age: range: 40–69 y	Gastric cancer detection rate (mucosal and submucosal carcinoma and high–grade intraepithelial neoplasia) Proportion of gastric cancers detected at an early stage	0.48% (60/12 453); excluding high–grade intraepithelial neoplasia: 0.37% (47/12 453); 100% (60/60)
Chen et al., 2016 [34]	Direct gastroscopy	China (Linzhou)	Case–control study	Sample size: cases: n=313 (individuals who died of gastric cancer), controls: n=1876; Sex distribution: 69% male; Age: range: 40–69 y	OR regarding reduction in gastric cancer mortality	OR: 0.72 (95% CI 0.54–0.97)

HR – hazard ratio, n – number, n.r. – not reported, OR – odds ratio, PLs – precancerous lesions, RR – relative risk, y – year

Colombia [12], Mexico [18], Turkey [23] and Iran [25]. The follow–up period ranged between 1–15 years. Nine studies used anti–*H. pylori* treatment [13,14,16–18,22,25,26] only, and six studies also considered other substances eg, vitamins, garlic, celecoxib [12,15,19–21,24]. The antibiotics regimens used for anti–*H. pylori* treatment varied across studies. Gastric cancer incidence and mortality tended to be reduced by 40–50% [15,17,20]. The study by Guo et al. treating high risk subjects with antibiotics and Chinese herb medicine suggested a statistically significant reduction in gastric cancer mortality (RR = 0.50, 95% CI 0.34–0.73) at 3 years follow–up [15]. The study by Ma et al. found a statistically significant reduction in gastric cancer incidence (odds ratio (OR) = 0.61, 95% CI 0.38 – 0.96) but not in mortality 15 years after anti–*H. pylori* treatment [20]. A subgroup analysis of the same study restricted to persons ³55 years or older found a statistically significant reduction in gastric cancer incidence (OR = 0.36, 95% CI 0.17–0.79) and mortality (hazard ratio (HR) = 0.26, 95% CI 0.09–0.79) [21]. This study also found a reduction in gastric cancer incidence in persons with precancerous lesions (OR = 0.56, 95% CI 0.34 – 0.91)[1], while the study by Wong et al. only found such an effect in persons without precancerous lesions (*P* = 0.02) [17]. Of the studies investigating the impact of anti–*H.pylori* treatment on precancerous lesions [12–14,16,25,29], four differentiated according to the type of lesions and found a regression mainly for atrophy while there was no or only a marginal effect regarding intestinal metaplasia [12,14,16,25]. Apart from anti–*H. pylori* treatment, one study using a factorial design suggested an effect regarding regression of precancerous lesions also for celecoxib (OR = 1.50, *P* = 0.067) [24].

Studies on gastric cancer screening considered reduction in gastric cancer mortality or intermediate outcomes (eg, gastric cancer detection rate) as outcomes. Observational studies suggested a statistically significant reduction of gastric cancer mortality for direct gastroscopy (odds ratio (OR) = 0.72, 95% CI 0.54 – 0.97) and X–ray (48–59%, *P*<0.05) [30,34]. Screening with photofluorography was not found to reduce mortality from gastric cancer [29]. In the two studies on gastric cancer screening evaluating an occult blood bead detector (a device that is swallowed and then retrieved to detect occult blood in the stomach) the positivity rate ranged between 7–24% and the proportion of early stages of gastric cancers ranged between 45–85% [27,28]. With gastroscopy, proportion of gastric cancers detected at an early stage ranged between 60–100% [31–33].

Liver cancer

Studies on liver cancer prevention could be classified into three main categories: hepatitis B virus (HBV) immunization (2 randomized trials, 2 cohort studies, 1 intervention trial and 2 cross–sectional studies), liver cancer screening (2 randomized trials and 1 screening pilot study) and supplementation with minerals (1 non–randomized and 2 randomized trials). **Table 2** summarizes information from these studies [35–58].

Almost all HBV immunization studies assessed the effect of HBV vaccine in protecting against hepatitis B chronic carriage [35–47,49,50]. Two studies evaluated reduction in incidence of liver cancer in children and young adults [38,48]. All studies used plasma–derived hepatitis B vaccines except for one study [45] that used both plasma–derived and recombinant vaccines. Vaccination regimens varied widely in terms of dosage, number of vaccinations and time intervals between vaccinations. Reported follow–up period ranged between 1–30 years.

Reduction in the incidence of Hepatitis B surface Antigen (HBsAg) carrier state (ie, protection against chronic carriage) was consistently shown across studies, ranging between 65%–95% compared to non–vaccinated controls, and the effect remained stable during follow–up [35–47,49,50]. A cluster–randomized trial on HBV vaccination in newborns suggested a statistically significant reduction in liver cancer incidence in younger adults (HR = 0.16 (95% CI 0.03–0.77) and similarly, an incidence reduction was observed in a retrospective cohort study (*P* = 0.007) [38,48].

One study evaluated the effect of four combinations of various vitamins and minerals (eg, retinol and zinc or vitamin C and molybdenum etc.) regarding reduction of liver cancer mortality and did not show statistically significant effect [53]. Two studies conducted in China evaluated the effect of supplementation of selenium regarding liver cancer incidence in the general population and in HBsAg carriers. They suggested a reduction in age–adjusted incidence over time in the intervention group as compared to the control but it was not reported whether this was statistically significant [51,52].

Two studies investigated biannual testing of serum alpha fetoprotein to screen for liver cancer in high–risk subjects [54–57]. One study reported a statistically significant reduction in liver cancer mortality by 40% after 5 years of follow–up (RR = 0.63, 95% CI 0.41–0.98) [56]. The other study, however, did not

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Table 2. Studies investigating strategies for prevention of liver cancer

Author(s), year	Preventive measure/screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results
	HBV immunization:					
Maupas et al., 1981 [35]	HBV immunization with: 10 µg HBVD; Vaccination regimen: 3 times at one month intervals	Senegal (Niakhar)	Cluster-randomized controlled trial	Sample size: n=602; Sex distribution: 49% male; Age: range: 0–2 y	Reduction in incidence of HBsAg carrier state in susceptible children (seronegative and anti-HBc alone) at 1 y follow-up	85% (P<0.005)
Sun et al., 1986 [36]; Sun et al., 1991 [37]; Qu et al., 2014 [38]	HBV immunization with: 5 µg HBVD+HBIG; 5 µg HBVD; 2.5 µg HBVD+HBIG; 2.5 µg HBVD. Vaccination regimen: 3 times at 0, 1 and months after birth.	China (Qidong)	Cluster-randomized controlled trial	Sample size: n=1703; Sex distribution: 50% male; Age: new-born infants	Reduction in incidence of HBsAg carrier state: determined at 1 y and 5 y follow-up	**1 y follow-up:** 5 µg HBVD+HBIG: 85%; 5 µg HBVD: 83%; 2.5 µg HBVD+HBIG: 65%; 2.5 µg HBVD: 85% **5 y follow-up:** 5 µg HBVD+HBIG: 86%; 5 µg HBVD: 80%; 2.5 µg HBVD+HBIG: 62%; 2.5 µg HBVD: 75%
	HBV immunization with: 5µg HBVD; Vaccination regimen: 3 times at 0, 1 and 6 months after birth; booster dose after 10 to 14 y.	China (Qidong)	Cluster-randomized controlled trial	Sample size: n=73733; Sex distribution: 51% male; Age: new-born infants	Reduction in incidence of HBsAg carrier state determined at 18 y; determined at 30 y follow up. HR regarding liver cancer incidence rate at 30 y follow-up	78% (95% CI 75–80%); 72% (95% CI 68–75%); HR: 0.16 (95% CI 0.03–0.77)
Chotard et al., 1992 [39]; Fortuin et al., 1993 [40]; Viviani et al., 1999 [41]; Van der Sande et al., 2007 [42]; Peto et al., 2014 [43]	HBV immunization with: 10 µg HBVD; Vaccination regimen: 4 times at 0, 1, 4 and 9 months after birth	Gambia	Cohort study among vaccinated children combined with a cross-sectional survey among unvaccinated children	Sample size: n=1000; Sex distribution: n.r.; Age: children that received HBV vaccine in infancy	Reduction in incidence of HBsAg carrier state determined at 3 y follow-up; determined at 4 y follow-up; determined at 9 y follow-up; determined at 15 y follow-up;	95% (95% CI n.r.); 94% (95% CI 84–98%); 94% (95% CI 84–98%); 97% (95% CI 91.5–100%)
			Cross-sectional study	Sample size: n=2670; Sex distribution: 44% male; Age: 17–21 y (birth years 1986–90)	Reduction in incidence of HBsAg carrier state determined at 21 y follow-up	94% (95% CI 77–99%)
Whittle et al., 1991 [44]; Whittle et al., 1995 [45]; Whittle et al., 2002 [46]; Mendy et al., 2013 [47]	HBV immunization with varied HBVDs (2, 2.5, 5, 10 and 20 µg) and different vaccination regimens (3 or 4 times between 0–4 y)	Gambia (Keneba & Manduar)	Intervention trial	Sample size: n=856 (continued recruitment); Sex distribution: n.r.; Age: range: 0–4 y	Reduction in incidence of HBsAg carrier state determined at 4 y follow-up; determined at 8 y follow-up; determined at 14 y follow-up; determined at 24 y follow-up	97% (95% CI 91.0–99.2%); 95% (95% CI 91.0–97.5%); 94% (95% CI 89–97%); 95% (95% CI 91.5–97.1%)
Wichajarn et al., 2008 [48]	HBV immunization	Thailand (Khon Kaen)	Retrospective cohort study	Sample size: n=n.r. (newborns in Khon Kaen); Sex distribution: n.r.; Age: newborns	Age-standardized incidence rate of hepatocellular carcinoma in vaccinated vs non-vaccinated children aged 5–18 y	Non-vaccinated: 0.97 per million; vaccinated: 0.24 per million (P=0.007)
Shen et al. 2011 [49]	HBV immunization	China (Long An)	Cross-sectional study	Sample size: n=4686; Sex distribution: 49% male; Age: range: 0.25–60 y; median: 34 y	Rate of HBsAg seroprevalence in subjects born before vs after start of the HBV vaccination programme (<20 vs ≥20 y)	≥20 y: 10.5% (95% CI 9.4–11.7%); <20 y: 2.4% (95% CI 1.7–3.1%)

Table 2. Continued

Author(s), year	Preventive measure/screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results
Postuwan et al., 2016 [50]	HBV immunization	Thailand	Cross–sectional study	Sample size: n=5964; Sex distribution: n.r.; Age: range: 0.5–60 y	Rate of HBsAg seroprevalence in subjects born before vs after start of the HBV vaccination programme (<22–24 y vs ≥22–24 y; exact cutoff depending on region)	≥22–24 y: 4.5%; <22–24 y: 0.6%; (P=0.001)
Supplementation with minerals:						
Yu et al., 1991 [51]; Yu et al., 1997 [52]	Daily supplementation of: selenium fortified salt in the general population. Duration of supplementation: 8 y	China (Qidong)	Placebo–controlled trial with intervention and control communities	Sample size: n=130471; Sex distribution: n.r.	Age-adjusted incidence of primary liver cancer in the intervention vs control group before and after the trial	Intervention group: before trial: 42/100000; after trial: 27/100000. Control group: no change
	Daily supplementation of: selenized yeast tablets in HBsAg carriers. Duration of supplementation: 4 y	China (Qidong)	Randomized placebo–controlled trial	Sample size: n=226 (HBsAg carriers); Sex distribution: n.r.; Age: range: 21–63 y	Incidence of primary liver cancer in the intervention vs the control group determined at the end of the trial	Intervention group: 0/113. Placebo group: 7/113
Qu et al., 2007 [53]	Daily supplementation of: Factor A (retinol+zinc); Factor B (riboflavin+niacin); Factor C (vitamin C +molybdenum); Factor D (beta–carotene+vitamin E + selenium) Duration of supplementation: 5.25 y	China (Linxian)	Randomized trial with 2^4 factorial design	Sample size: n=29450; Sex distribution: 45% male; Age: range: 40–69 y	HR regarding reduction of liver cancer mortality determined at 15 y follow–up	Factor A: 0.86 (95% CI 0.62–1.18); Factor B: 0.86 (95% CI 0.62–1.18); Factor C: 0.84 (95% CI 0.61–1.16); Factor D: 0.81 (95% CI 0.59–1.12)
Early detection:						
Yang et al., 1997 [54]; Zahng et al., 1999 [55]; Zahng et al., 2004 [56]	Biannual testing of serum alpha–fetoprotein	China (Shanghai)	Randomized controlled study	Sample size: n=18816 (HBV infected or history of chronic hepatitis); Sex distribution: 63% male; Age: range: 35–55 y; mean: 53 y	Reduction in liver cancer mortality determined at 5 y follow–up (after 5–10 screening rounds)	RR: 0.63 (95% CI 0.41–0.98)
Chen et al., 2003 [57]	Biannual testing of serum alpha-fetoprotein for 62 months	China (Qidong)	Randomized controlled study	Sample size: n=5581 (HBsAg carriers); Sex distribution: 100% male; Age: range: 30–69 y; mean: 41 y	Liver cancer detection rate; Proportion of liver cancers detected at an early stage; Reduction in liver cancer mortality determined 6 y after start of the trial	7% (374/5581); 28% (67/240) (screen group); 4% (4/108) (control group); (P<0.0001); 1138/1000000 (screen group); 1114/100000 (control group); (P=0.86)
Eltabbakh et al., 2015 [58]	Biannual testing of serum alpha–fetoprotein and ultrasonography of liver for at least 18 months	Egypt	Screening pilot study	Sample size: n=1286 patients with liver cirrhosis undergoing screening); Sex distribution: 35% male; Age: >18 y, mean: 51 y	Liver cancer detection rate; Proportion of liver cancers detected at an early stage in the screening cohort as compared to 155 symptomatic liver cancer patients	8% (102/1286); 89% (91/102) (screen–detected patients); 22% (35/155) (symptomatic patients) (P<0.0001)

Anti–HBc – hepatitis B core antibody, HBIG – Hepatitis B virus immune globulin, HBsAg – hepatitis B surface antigen, HBV – hepatitis B virus, HBVD – hepatitis B vaccine dose, HR – hazard ratio, n – number, n.r. – not reported, OR – odds ratio, y – year

suggest a statistically significant reduction in liver cancer mortality ($P = 0.86$). One study evaluated combination of biannual testing of serum alpha fetoprotein and liver ultrasonography to screen for liver cancer and reported that the proportion of liver cancers detected at an early stage was 90% [58].

Colorectal cancer

With respect to CRC prevention, 18 screening studies conducted mainly in average–risk subjects were identified. They investigated colonoscopy (6 cross–sectional diagnostic studies and 1 screening pilot study), rectoscopy (1 cross–sectional diagnostic study and 1 cohort study with external control group), and fecal occult blood testing (2 cross–sectional diagnostic studies and 7 screening pilot studies). **Table 3** summarizes information about these studies [59–76].

In colonoscopy studies, CRC detection rates were between 0.5–6% [61–67]. One study assessed proctoscopy with regular endoscopic follow–up of persons in whom precursor were removed. It suggested a reduction in rectal cancer incidence and mortality of 31% and 18% at 20 years follow–up, respectively, when compared to an external control group [60]. Three studies reported a participation rate above 40% for colonoscopy in first–degree relatives of CRC patients [62,63,66].

In studies on fecal occult blood testing, CRC detection rates were directly associated with positivity rates in five of six studies [68,70–74]. The lowest CRC detection rate (0.06%) was reported from a study on sequential fecal occult blood testing [68]. The highest positivity rates were reported from studies using fecal immunochemical testing for hemoglobin (FIT) [70–74]. The proportion of early stages among detected CRCs ranged between 47–94% [68,70–72]. Two studies investigated the potential of risk stratification using a clinical risk score combined with FIT [75,76]. One of these studies found a five–fold higher rate of advanced neoplasia among those with both a high–risk score and a positive FIT result as compared to those with a moderate–risk score and a negative FIT result [76]. The other study, a cluster–randomized study, suggested a reduction in CRC mortality after 8 years follow–up [75]. Five studies reported participation rates for fecal occult blood testing above 60% [68,70,72–74].

DISCUSSION

Our systematic review identified a wide range of studies evaluating strategies for prevention of GICs in developing countries, including follow–up reports up to 30 years. Studies on gastric and liver cancer prevention showing promising results only after long–term follow–up illustrate the particular challenge of generating evidence in cancer prevention.

The development and evaluation of strategies for cancer prevention is a long–lasting process. The duration of this process is amongst others determined by the natural history of the disease, ie, the time that it takes until risk factors, precursor lesions or preclinical cancer stages would have impacted on the disease incidence or mortality if they had remained unchanged or untreated. If the interruption of the natural history takes place at an early phase in life, the time lag until a potential effect is measurable at the population level is further prolonged.

The studies included in our review on anti–*H. pylori* treatment to prevent gastric cancer can be considered as an example where the process of developing a preventive strategy takes long. With a follow–up time of 7.5 years after *H. pylori* treatment the randomized controlled trial by Wong et al. found an incidence reduction of 40% for gastric cancer but this effect did not reach statistical significance [17]. With a follow–up time of 15 years Ma et al. found a similar effect that was statistically significant. Regarding the effectiveness of anti–*H. pylori* treatment in persons who already have precancerous lesions the evidence is still not conclusive. Some but not all studies found a regression of precancerous lesions after *H. pylori* treatment. One study reported a preventive effect only in subgroup analysis restricted to persons without precancerous lesions [17]. A recent study by Li et al. analyzing 15–year follow–up data suggested a reduction in the incidence of gastric cancer by 40% among subjects with intestinal metaplasia and dysplasia treated against *H. pylori* at baseline [21]. As for vaccination programs, *H. pylori* treatment is a preventive measure that can be completed within a narrow time window and does not need to be repeated on a regular basis, which is an important aspect in view of large–scale feasibility and acceptance.

The studies included in our review on HBV vaccination published in 1981 and later can be considered as an example where the process to develop a preventive strategy that is widely accepted and applied was relatively short. Robust evidence showed that vaccine efficacy against chronic carriage of HBV was as high as 65–95% across studies and remained stable with time. Since 1992 the World Health Organization

Table 3. Studies investigating strategies for prevention of colorectal cancer

Author(s), year	Preventive measure/ screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results
Colonoscopy screening						
Zheng et al., 1991 [59]	Rectoscopy (alone or in combination with fecal occult blood testing)	China (Jiashan)	Cross–sectional diagnostic study	Sample size: n=26 171; Sex distribution: n.r.; Age: 330 y	Polyp detection rate; Rectal cancer detection rate; Proportion of rectal cancers detected at an early stage	3% (899/26 171); 0.05% (15/26 171); 53% (8/15)
Zheng et al., 2002 [60]	Proctoscopy. Endoscopic follow–up of individuals with removed precursor lesions every 2–5 y	China (Haining)	Cohort study with external control group	Sample size: n=4072; Sex distribution: 64% male; Age: range: 30–70 y; mean: 50 y	Standardized incidence ratio and standardized mortality ratio determined at 20 y follow–up	Rectal cancer Standardized incidence ratio: 0.69; Standardized mortality ratio: 0.82. Colon cancer: no effect was observed.
Wan et al., 2002 [61]	Colonoscopy	China	Cross–sectional diagnostic study	Sample size: n=2196 (74% were asymptomatic); Sex distribution: 94% male; Age: range: 60–90 y; average: 70 y	Polyp detection rate; CRC detection rate; Proportion of CRCs detected at an early stage	62% (1364/2196); 2% (52/2196); 37% (19/52)
Croitoru et al., 2010 [62]	Colonoscopy	Romania (Suceava & Iasi)	Cross–sectional diagnostic study	Sample size: n=102; (all asymptomatic and with at least one first–degree relative with CRC); Sex distribution: 57% male; Age: range: 36–72 y; mean: 52 y	Participation rate; CRC detection rate; Proportion of CRCs detected at an early stage	47% (102/216); 2% (2/102); 50% (1/2)
Arafa et al., 2011 [63]	Colonoscopy	Jordan (Hashemite)	Cross–sectional diagnostic study	Sample size: n=95 (symptomatic first degree relatives of CRC patients); Sex distribution: 61% male; Age: range: 40–75 y; mean: 53 y	Participation rate; Polyp detection rate; CRC detection rate; Proportion of CRCs detected at an early stage	62% (95/153); 11%(10/95); 2% (2/95); 100% (2/2)
Aswakul et al., 2012 [64]	Colonoscopy	Thailand	Cross–sectional diagnostic study	Sample size: n=1594 (asymptomatic average and high risk individuals); Sex distribution: 45% male; Age: mean: 58 y	Adenoma detection rate; Advanced adenoma detection rate; CRC detection rate	16% (263/1954); 3% (43/1594); 0.6% (10/1594)
Ionescu et al., 2015 [65]	Colonoscopy	Romania (Bucharest)	Cross–sectional diagnostic study	Sample size: n=1087 (average risk individuals); Sex distribution: 47% male; Age: range: 23–97 y; mean: 58 y	Adenoma detection rate; Advanced adenoma detection rate; CRC detection rate	13% (228/1807); 6% (110/1807); 3% (61/1807)
Panic et al., 2015 [66]	Colonoscopy	Montenegro	Cross–sectional diagnostic study	Sample size: n=540 (first–degree relatives of CRC patients); Sex distribution: 41% male; Age: >40 y or 10 y before index case age	Participation rate; Adenoma detection rate; Advanced adenoma detection rate; CRC detection rate	76% (540/710); 28% (151/540); 11% (58/540); 6% (31/540)
	FIT	Montenegro	Cross–sectional diagnostic study	Sample size: n=920 (average risk individuals); Sex distribution: 51% male; Age: range: 50–74 y	Participation rate; Adenoma detection rate; Advanced adenoma detection rate; CRC detection rate	33% (920/2760); 3% (26/920); 2% (19/920); 1% (5/920)
Siripongpreeda et al., 2016 [67]	Colonoscopy	Thailand	Screening pilot study	Sample size: n=1404 (average–risk); Sex distribution: 31% male; Age: mean: 57 y	Participation rate; Adenoma detection rate; Advanced adenoma detection rate; CRC detection rate; Proportion of CRCs detected at an early stage	87% (1404/1612); 18% (256/1404); 7% (98/1404); 1% (18/1404); 89% (16/18)

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Table 3. Continued

Author(s), year	Preventive measure/screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results
Li et al. 2003 [68]	Sequential FOBT (guaiac FOBT followed by FIT)*	China (Beijing)	Screening pilot study	Sample size: n=19852; Sex distribution: 51% male; Age: mean: 50 y	Participation rate; Positivity rate; Polyp detection rate; CRC detection rate; Proportion of CRCs detected at an early stage	74% (19852/26827); 3% (501/19852); 1% (188/19852); 0.06%(12/19852); 92% (11/12)
Li et al. 2006 [69]	Guaiac FOBT, FIT, sequential FOBT (comparative evaluation)*	China (Beijing)	Cross-sectional diagnostic study	Sample size: n=323 (patients referred for colonoscopy); Sex distribution: 57% male; Age: range: 18–68 y; mean: 53 y	Sensitivity and specificity of guaiac FOBT, FIT and sequential FOBT regarding CRC	See sub-table below
Fenocchi et al., 2006 [70]	FIT	Uruguay (Montevideo)	Screening pilot study	Sample size: n=10573 (average-risk); Sex distribution: 31% male; Age: mean: 61 y	Participation rate; Positivity rate; Proportion of test positives undergoing colonoscopic follow-up; CRC detection rate; Proportion of CRCs detected at an early stage	90% (10573/11734); 11% (1,170/10573); 75% (879/1170); 1% (101/10573); 47%(47/101)
Yang et al., 2011 [71]	FIT	China (Shanghai)	Screening pilot study	Sample size: n=5919; Sex distribution: 55% male; Age: mean: 55 y	Positivity rate; Proportion of test positives undergoing FIT follow-up; CRC detection rate; Proportion of CRC detected at an early stage; Adenoma detection rate	5% (314/5919); 84% (264/314); 0.2% (16/5919); 94% (15/16); 1% (94/5919)
Khuhamprema et al., 2014 [72]	FIT	Thailand (Lampang)	Screening pilot study	Sample size: n=127301; Sex distribution: 46% male; Age: range: 50–65 y	Participation rate; Positivity rate; Proportion of test positives undergoing colonoscopic follow-up; CRC detection rate; Proportion of CRC detected at an early stage; A denoma detection rate	63% (80012/127301); 1% (873/80012); 72% (627/873); 4% (23/627); 61% (14/23); 30% (187/627)
Dimova et al., 2015 [73]	FIT	Bulgaria	Screening pilot study	Sample size: n=600 (average-risk); Sex distribution: 45% male; Age: mean: 61 y	Participation rate; Positivity rate; Proportion of test positives with information on colonoscopy; CRC detection rate	79% (473/600); 8% (40/473); 75% (30/40); 0.6% (3/473)

Results sub-table for Li et al. 2006 [69]:

Test	Two-sample		Three-sample	
	Sensitivity	Specificity	Specificity	Specificity
FIT	88%	96%	96%	89%
Guaiac FOBT	78%	89%	96%	76%
Sequential FOBT	76%	99%	94%	94%

Table 3. Continued

Author(s), year	Preventive measure/ screening tool	Country (region)	Study design	Study population	Outcome(s) under study	Results
Bankovic et al., 2016 [74]	FIT	Serbia	Screening pilot study	Sample size: n=99 592; Sex distribution: n.r.; Age: range:50–74 y	Participation rate; Positivity rate; Proportion of test positives undergoing colonoscopic follow–up; CRC detection rate; Adenoma detection rate	62% (6252/99592); 6% (3690/62252); 42% (1554/3690); 8% (129/1554); 38% (586/1554)
Zheng et al., 2003 [75]	Step 1: Risk stratification based on clinical score combined with FIT result; Step 2: Flexible sigmoidoscopy	China (Jiashan)	Cluster–randomized screening pilot study	Sample size: n=62 677 (average – risk); Sex distribution: 51% male; Age: ≥30 y	Positivity rate; Polyp detection rate; CRC detection rate; Proportion of CRC detected at an early stage; Mortality and incidence rate of CRC in the screening vs control group at 8 y follow–up	7% (4299/62677); 0.5% (331/62677); 0.03% (21/62677); 71% (15/21); **Mortality rate:** 208/100 000 (95% CI 196–218/100000) (screening group); 244/100 000 (95% CI 233–255/100000) (control group); **Incidence rate:** 395/100 000 (95% CI 381–410/100000) (screening group); 401/100 000 (95% CI 386–411/100000) (control group)
Aniwan et al., 2015 [76]	Step 1: Risk stratification based on clinical score combined with FIT result; Step 2: Colonoscopy	Thailand (Bankok)	Cross–sectional diagnostic study	Sample size: n=948 (average risk); Sex distribution: 35% male; Age: range: 50–75 y; mean: 61 y	Polyp and CRC detection rate	*(see table below)*

Category	Non-advanced neoplasia	Advanced neoplasia	CRC
High risk score and positive FIT (n=84)	44%	37%	5%
High risk score and negative FIT (n=173)	30%	12%	1%
Moderate risk score and positive FIT (n=192)	27%	12%	2%
Moderate risk score and negative FIT (n=499)	23%	6%	0%

CRC – colorectal cancer, FIT – fecal immunochemical testing for hemoglobin, FOBT – fecal occult blood testing, n – number, n.r. – not reported, y – year

*Sequential FOBT was called a sequential method that combined guaiac FOBT and FIT, ie, guaiac FOBT was performed first and FIT was only performed if the guaiac FOBT was positive. The result was interpreted as positive if both tests were positive.

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(WHO) has recommended that all infants receive the HBV vaccine as soon as possible after birth. As of 2013, 183 WHO member states have included HBV vaccination in their preventive programs [77]. While the various beneficial effects of these programs regarding HBV–related diseases are out of question, it will take more time to see their full effect on incidence and mortality of liver cancer, particularly in adults. The study by Wichajarn et al. [48] already observed an incidence reduction for hepatocellular carcinoma among children in Thailand, which confirms earlier reports from Taiwan [78]. A study from China reported an incidence reduction of 84% in a study population that reached early adulthood [38]. This also confirms earlier reports from Taiwan showing that the preventive effect of HBV vaccination extends from childhood to early adulthood [79].

Studies included in our review on the prevention of gastric and liver cancer by supplementation of vitamins or minerals in developing countries give the impression that there is a lack of effectiveness or not enough evidence yet to justify their translation into a preventive program. Most studies did not show an effect or were difficult to interpret. This is in line with results of supplementation trials conducted in Western countries that did not show beneficial effects either, such as the Selenium and Vitamin E Cancer Prevention Trial [80]. Apart from the lack of effectiveness, it is questionable whether preventive measures that require long–term and regular use of supplements would prove suitable for developing countries. Food or soil fortification may have more potential in terms of practicality, but of course this would become relevant only for measures with proven effectiveness and safety [81].

Practicality is also an important aspect to be discussed in the context of cancer screening in developing countries. The screening strategies included in this review, mainly focused on colorectal cancer, which is less amenable to primary prevention through risk factor modification as compared to gastric and liver cancer. Implementing population–based screening programs may be challenging in developing countries in view of resource constraints (eg, infrastructure, availability of equipment and trained personnel, costs). This notion is supported by the fact that substantial proportion of screening studies has been conducted in China that has more resources than many other developing countries. While most screening studies were limited to intermediate endpoints (eg, detection rates), Zahng et al. reported a reduction in liver cancer mortality by 40% for biannual serum alpha–fetoprotein testing in high risk groups (HBV infected or history of chronic hepatitis) after 5–10 screening rounds [56]. Targeting screening at high–risk groups rather than at average–risk persons may generally be a more doable approach for developing countries that seems worthwhile to be further explored, eg, also for colorectal cancer. To ensure practicality of such strategies, identification of risk groups needs to be based on easily obtainable information (eg, family history, lifestyle or basic clinical factors). This was exemplified by two studies that used a clinical risk score combined with FIT to identify risk groups that benefit most from colonoscopy [75,76]. However, when estimating the effectiveness of potential screening strategies in developing countries, the treatability of early cancer stages also requires consideration. In industrialized countries, an important argument in favor of screening is the better prognosis for early vs late stages, but this may not hold true in developing countries if, for example, surgical treatment options are limited [82].

To the best of our knowledge, there is no similar review that systematically summarizes studies on the prevention of gastric, liver and colorectal cancer in developing countries including long–term follow–up reports on these studies. Considerable variation in prevalence of various cancers between low– and high–resource countries, extensive differences in operational settings and possibly also in compliance rates warrant to put a focus on strategies for cancer prevention specifically in developing countries. There are also limitations that should be noted. First, our search was restricted to papers published in English and we did not optimize our search for specific sub–questions such as HBsAg carrier state nor did we include the aspect of cost–effectiveness. Second, incomplete reporting of relevant information in original articles partly limited interpretability of the studies. Third, our review provides a descriptive summary of studies, while meta–analyses would have been beyond its scope. However, we consider our review an important pre–work that will facilitate the planning and conduct of such meta–analyses, particularly by providing information regarding heterogeneity between studies (in terms of the study designs, the target populations, the interventions, the follow–up periods, the outcomes etc.). Fourth, as for any review, we cannot rule out that publication bias has led to overestimating the beneficial effect of preventive measures. In the interpretation of this review it should also be noted that almost half of the studies were conducted in China, but developing countries considerably vary in their Human Development Index and aspects of effectiveness and feasibility may not be similar across countries.

In conclusion, there were a number of studies on gastric and liver cancer prevention in developing countries showing promising results after long–term follow–up. Important next steps include pooled meta–analyses as far as possible given the heterogeneity between studies as well as implementation research.

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Factors associated with physical violence by a sexual partner among girls and women in rural Kenya

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Background Intimate partner physical violence increases women's risk for negative health outcomes and is an important public health concern. The purpose of the present study was to determine 1) the proportion of girls (≤18 years) and women (>18 years) who experienced physical violence by a sexual partner, and 2) factors (including self–reported HIV infection) associated with girls and women who experienced physical violence by a sexual partner.

Methods Cross–sectional surveys conducted in the Gem Health and Demographic Surveillance System (HDSS) area in Siaya County, western Kenya in 2011–2012 (Round 1) and 2013–2014 (Round 2).

Findings Among 8003 unique participants (582 girls and 7421 women), 11.6% reported physical violence by a sexual partner in the last 12 months (girls: 8.4%, women: 11.8%). Three factors were associated with physical violence by a sexual partner among girls: being married or cohabiting (nearly 5–fold higher risk), low education, and reporting forced sex in the last 12 months (both with an approximate 2–fold higher risk). Predictive factors were similar for women, with the addition of partner alcohol/drug use and deliberately terminating a pregnancy. Self–reported HIV status was not associated with recent physical violence by a sexual partner among girls or women.

Conclusions Gender–based physical violence is prevalent in this rural setting and has a strong relationship with marital status, low education level, and forced sex among girls and women. Concerted efforts to prevent child marriage and retain girls in school as well as implementation of school and community–based anti–violence programs may help mitigate this risk.

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Intimate partner violence (IPV), where an individual (mostly, but not exclusively, a male) causes physical, sexual, or emotional abuse to their partner, occurs worldwide and has serious physical health and psychological consequences [1]. Moreover, IPV against women can contribute to an increased risk for HIV directly through forced sex or indirectly, for example, through power inequity in negotiating condom use [2], or an increase in risk behaviors such as substance abuse [3]. In addition, women who experience IPV may not receive needed health care, including regular HIV testing [4]. An analysis of the 2008–2009 Demographic and Health Survey [5] in Kenya found a significant association between IPV and HIV infection, controlling for sociodemographic and other risk factors [6]. Importantly, studies have found that culturally–based gender inequalities, including

power and resource distribution, contribute to an environment that fosters high levels of IPV and HIV infection [7].

Adolescent girls are at a greater risk of HIV infection compared to their male age–mates in lower and middle income countries [8]. Our aim was to better understand the dynamics of risk for physical violence (eg, hitting, slapping, kicking) by a sexual partner and associated factors among girls separately from women. Our setting was Siaya County, western Kenya, where HIV prevalence is high (estimated 24.8% among persons 15–49 years of age) [9]. Specifically, the purpose of the present study was to determine 1) the proportion of girls (≤18 years of age) and women (>18 years of age) who experienced physical violence by a sexual partner, and 2) factors (including self–reported HIV status) associated with girls and women who experienced physical violence by a sexual partner.

METHODS

Design

Two cross–sectional surveys evaluating HIV risk behaviors, HIV sero–status factors, HIV prevention services and care and treatment uptake were conducted within the Kenya Medical Research Institute (KEMRI) Health and Demographic Surveillance System (HDSS) area in Gem, located in Siaya County in rural western Kenya. The KEMRI HDSS offered a sampling frame of all the registered housing compounds (14 501 in 2010). A compound is a cluster of houses usually occupied by households of the same extended family and usually demarcated by a fence. A random sample of 4000 compounds was selected through a community–based simple random approach. This entailed all compounds in the village being given a unique registration number, thus there was no possibility of sampling bias.

Compounds were randomly chosen by a combination of methods: community participation which included community leaders (n = 25) picking pieces of paper from a bucket and the study statistician picking random numbers via a computer until a total sampling frame of approximately 6000 compounds was identified. Trained field staff visited each compound; all households within the compound were approached and all individuals aged 13 years and above who had slept there the prior night and gave informed consent were interviewed. All eligible persons were verbally informed of the study, and if in agreement then provided written consent (see Ethics section). The two surveys took place March 2011 to September 2012, and January 2013 to April 2014, respectively. The survey targeted 15 000 individuals. Persons who were not residents of the HDSS, but who slept in the sampled compound the night prior to the survey date, were also enrolled and interviewed as long as they met the inclusion criteria and provided informed consent. The intention was to interview the same persons in the sampled housing compounds during Round 1 and Round 2 in order to develop a community–based platform to evaluate various infectious and non–infectious disease interventions. However due to in–migrations and out migrations experienced in the HDSS, not all respondents in Round 1 were interviewed in Round 2 and vice versa, as well as people simply not found at home.

Study location and population.

The HDSS was launched in September 2001 by the US Centers for Disease Control and Prevention in collaboration with KEMRI, and provides general demographic and health information, as well as disease and intervention information, in western Kenya. Gem HDSS area is located about 20 km northeast of Lake Victoria in Siaya County, formerly Siaya District. Residents are predominately of Luo ethnicity, and their major economic activity is subsistence farming [10]. The mid–year population in Gem in 2012 was 86 279 across 21 131 households grouped by extended families into 14 954 compounds. Females comprised approximately half (52.5%) of the population [11]. The area experiences substantial in and out migration, in part due to young men seeking employment in the nearby city of Kisumu and beyond, and the traditional exogamous marriage system where persons marry outside of the group to which they belong.

HIV risk behavioral survey

Using the Gem HDSS as a sampling frame, a questionnaire focusing on HIV risk behaviors and health service uptake was administered immediately before HIV testing and counseling to avoid knowledge of the HIV test result which could have influenced responses. The questionnaire targeted all persons in the household (males and females) meeting specific age criteria. Inclusion criteria were age ≥13 years, resi-

dent of Gem, and willing to give informed consent to participate in the survey. The questionnaire was structured and pre–coded and administered using a computer–assisted personal interview (CAPI). This was similar to a paper questionnaire because trained interviewers asked participants the questions and recorded their responses. Thus, even the few who were functionally illiterate could participate in the survey. The questionnaire was available in three languages, English, Kiswahili and Dholuo. Trained field staff used the HDSS household list to randomly select eligible household members for an interview. All interviews were conducted in the home privately. Interviewers were trained on the general interviewing techniques as well as on how to use Questionnaire Design Studio (QDS) for CAPI.

Measures

The dependent variable was female responses to the question, "Have any of your sexual partners in the last year hit/slapped/kicked or done anything else to hurt you physically in the last 12 months?" (herein referred to as "experienced physical violence by a sexual partner") (yes/no). It should be noted that emotional abuse was not captured in this question. Independent variables were chosen from the survey based on the existing literature and included age, highest level of education, source of income, marital status (henceforth married also includes cohabiting), number of pregnancies, ever deliberately terminated a pregnancy, lifetime number of sex partners, ever used a condom (yes/no), age at first sex, most recent self–reported HIV test result, would say yes/no to sex if they knew their partner had an STI, forced sex in last 12 months (yes/no) (refers to same last 12 months as physical violence by a sexual partner), and partner used alcohol before last sex and/or drug use in last 12 months (yes/no). For the last 3 independent variables, if the response was "yes" for any of the sexual partners the respondent had in the last 12 months, the variable was coded as a "yes". Because a large number of participants had missing HIV laboratory test results, we used self–reported HIV status. To ensure that self–reported HIV status was a valid measure, we examined a subset of persons in Round 1 who had both laboratory verified HIV test result and self–reported test results for degree of agreement. The kappa statistic was 0.87, which indicated that self–reported HIV status could be used as a substitute for the laboratory reported HIV result.

Ethics

All persons received information about the objectives of the study and were informed that the information they provided would be kept private, that they could choose not to participate, and that they would not be identified when the information was reported. Girls 13–17 years of age provided consent if they were independent mature minors (living with a consensual sexual partner, currently pregnant or already a mother). For non–mature minors, parental consent and child assent was required. Thus, informed consent or assent was obtained from all individual participants included in the study. Survey participants were given a bar of soap as a token of appreciation for their participation. All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol, consent forms, and data collection instruments were reviewed and approved by the Centers for Disease Control and Prevention and the KEMRI local and national Ethical Review Committees (SSC1801).

Analysis

We conducted descriptive analyses as well as bivariate and multiple regression analyses to determine factors associated with girls (≤18 years old) and women (>18 years old) who experienced physical violence by a sexual partner. Due to sparse numbers, we had to combine the responses to two questions regarding partner use of alcohol and partner use of drugs even though the time frames were different. We collapsed the data for number of pregnancies because there were not enough females with zero pregnancies to be able to code nulliparous as a separate category. In the first step of model selection, a bivariate model was applied which included only a single variable at a time to be associated with experiencing physical violence by a sexual partner. All candidate variables that had P–values ≤0.2 in the bivariate model were entered into the multivariable model selection. In developing a final multivariable model, backward selection was applied with a P–value less than 0.05 as the selection criterion. A robust Poisson model with sandwich standard error estimator (generated by generalized estimating equation [GEE]) was used to estimate the risk ratios (RR) in the bivariate models and adjusted risk ratios (aRR) in the multivariable models [12,13].

The intent was to re–interview the same persons in Round 1 and Round 2 and to interview persons in the sampled compounds in Round 2 who were not found during Round 1. However, due to immigration

and emigration, some persons who participated in the Round 1 survey were not available to participate in the Round 2 survey and persons were interviewed in Round 2 who did not participate in Round 1. Thus, we used GEE to control for the correlation between the two rounds of data. For the females who participated in Round 1 and Round 2, if the female reported having experienced physical violence by a sexual partner in Round 1, in Round 2 or in both, they were considered as having experienced physical violence by a sexual partner.

RESULTS

There were a total of 28 383 participants surveyed during the two study rounds, of whom 11 312 were male and thus removed from the analysis. Among the females, 3821 were removed because they did not answer the violence question. Finally, as we were interested in examining experience of physical violence by a sexual partner, we removed 3780 females who did not report ever having had sexual intercourse or who had not had sexual intercourse in the past 12 months. After accounting for duplicates (the same person interviewed in Rounds 1 and 2), the final number of unique participants was 8003 (**Figure 1**). Most women participated in only one of the two Rounds of data collected (Round 1 = 3831; Round 2 = 2705). There were 1467 females who participated in both Round 1 and Round 2.

The median age of the survey participants in our analysis was 31 (interquartile range (IQR) = 23, 42). The median age was 17 years old for girls in Round 1 with IQR (16, 18) and the same for Round 2. The median age was 32 years for women in Round 1 with IQR (25, 43) and also 32 years in Round 2 with IQR (25, 44). Nearly half of girls ≤18 years of age and more than 85% of women >18 years of age were married (**Table 1**). The youngest participant who reported being married was 13 years of age. Among 13–year–old participants in Round 1, 16.7% (2 of 12) were married and in Round 2, 14.3% (1 of 7) were married. Data in **Table 1** are based on total unique participants. The proportion of females who self–reported being HIV–positive was 13.5% in Round 1 (girls: 3.2%, women: 14.3%) and 15.2% in Round 2 (girls: 3.6%, women 15.8%).

Among the 8003 unique participants, a significantly higher proportion of women reported physical violence by a sexual partner than girls (girls: 8.4%, women: 11.8%; $P = 0.01$). Of the 3831 females who participated only in Round 1, 8.6% of girls and 14.7% of women experienced physical violence from a sexual partner. Of the 2705 females who participated only in Round 2, 7.4% of girls and 10.0% of women
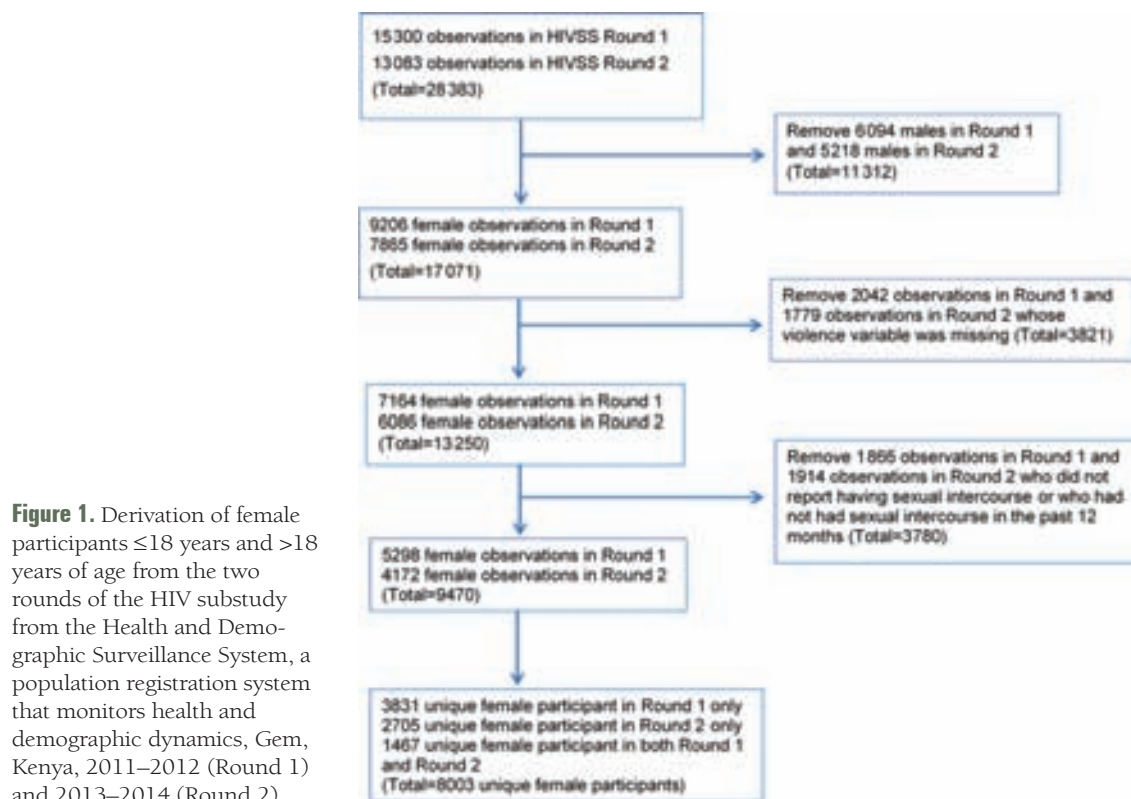
Figure 1. Derivation of female participants ≤18 years and >18 years of age from the two rounds of the HIV substudy from the Health and Demographic Surveillance System, a population registration system that monitors health and demographic dynamics, Gem, Kenya, 2011–2012 (Round 1) and 2013–2014 (Round 2)..

Table 1. Characteristics of female participants in Gem, Kenya, 2011–2012 (Round 1) and 2013–2014 (Round 2)*

	Round 1 (N = 5298)			Round 2 (N = 4172)		
	Total	≤18 y old (n=393)	>18 y old (n=4905)	Total	≤18 y old (n=223)	>18 y old (n=3949)
Median age in years (IQR)	31 (23, 42)	17 (16, 18)	32 (25, 43)	31 (24, 43)	17 (16, 18)	32 (25, 44)
Highest level of education (n, %):						
None	394 (7.4)	1 (0.3)	393 (8.0)	275 (6.6)	1 (0.5)	274 (6.9)
Primary incomplete and complete	3999 (75.5)	307 (78.1)	3692 (75.3)	3167 (75.9)	180 (80.7)	2987 (75.6)
Secondary incomplete and complete	826 (15.6)	83 (21.2)	743 (15.2)	663 (15.9)	42 (18.8)	621 (15.7)
Tertiary	79 (1.5)	2 (0.5)	77 (1.6)	67 (1.6)	0 (0.0)	67 (1.7)
Sources of income (cash) (n, %):						
None	669 (12.6)	98 (25.0)	571 (11.6)	783 (18.8)	77 (35.3)	706 (17.9)
Work/Business	3728 (70.4)	105 (26.7)	3623 (73.9)	2714 (65.2)	48 (22.0)	2666 (67.6)
Partner/Family	770 (14.5)	185 (47.1)	585 (11.9)	655 (15.7)	92 (42.2)	563 (14.3)
Other	130 (2.5)	5 (1.3)	125 (2.6)	11 (0.3)	1 (0.5)	10 (0.3)
Marital status (n, %):						
Single	478 (9.0)	198 (50.4)	280 (5.7)	395 (9.5)	123 (55.2)	272 (6.9)
Married	4391 (82.9)	192 (48.9)	4199 (85.6)	3474 (83.3)	98 (44.0)	3376 (85.5)
Divorced/Widowed/Separated	429 (8.1)	3 (0.8)	426 (8.7)	303 (7.3)	2 (0.9)	301 (7.6)
Number of pregnancies (n, %):						
0	324 (6.1)	143 (37.1)	181 (3.7)	322 (7.7)	89 (40.3)	233 (5.9)
1–2	1320 (25.0)	225 (58.3)	1095 (22.4)	1013 (24.4)	125 (56.6)	888 (22.5)
3–4	1291 (24.4)	6 (1.6)	1285 (26.3)	1044 (25.1)	6 (2.7)	1038 (26.4)
5 or more	2347 (44.4)	12 (3.1)	2335 (47.7)	1781 (42.8)	1 (0.5)	1780 (45.2)
Deliberately terminated a pregnancy (n, %):						
Yes	317 (6.4)	15 (6.3)	302 (6.4)	171 (4.4)	8 (6.0)	163 (4.4)
No	4623 (93.6)	223 (93.7)	4400 (93.6)	3678 (95.6)	125 (94.0)	3553 (95.6)
Lifetime number of sexual partners (n, %):						
1	762 (15.5)	150 (38.9)	612 (13.5)	746 (19.8)	86 (39.1)	660 (18.6)
2	1426 (29.0)	122 (31.6)	1304 (28.8)	1280 (34.0)	76 (34.6)	1204 (34.0)
3 or more	2730 (55.5)	114 (29.5)	2616 (57.7)	1739 (46.2)	58 (26.4)	1681 (47.4)
Ever used a condom (n, %):						
Yes	1794 (33.9)	247 (62.9)	1547 (31.6)	1414 (33.9)	141 (63.2)	1273 (32.3)
No	3498 (66.1)	146 (37.2)	3352 (68.4)	2753 (66.1)	82 (36.8)	2671 (67.7)
If you knew your partner had an STI would say no to sex (n, %):						
Yes	4507 (85.8)	323 (82.8)	4184 (86.1)	3152 (76.3)	162 (75.4)	2990 (76.4)
No	745 (14.2)	67 (17.2)	678 (13.9)	978 (23.7)	53 (24.7)	925 (23.6)
Forced sex last 12 months (n, %):						
Yes	1129 (21.3)	63 (16.0)	1066 (21.8)	368 (8.8)	20 (9.0)	348 (8.8)
No	4165 (78.7)	330 (84.0)	3835 (78.3)	3801 (91.2)	203 (91.0)	3598 (91.2)
Partner alcohol or drug use at last sex (last 12 months) (n, %):						
Yes	887 (18.0)	36 (10.0)	851 (18.6)	497 (12.0)	8 (3.6)	489 (12.5)
No	4045 (82.0)	325 (90.0)	3720 (81.4)	3648 (88.0)	213 (96.4)	3435 (87.5)
Age at first sex (n, %):						
≤15 years	2660 (50.2)	121 (30.8)	2539 (52.0)	2320 (55.6)	78 (35.0)	2242 (56.8)
>15 years	2683 (49.8)	272 (69.2)	2366 (48.2)	1852 (44.4)	145 (65.0)	1707 (43.2)
Self–reported HIV status (n, %):						
Positive	645 (13.5)	11 (3.2)	634 (14.3)	605 (15.2)	7 (3.6)	598 (15.8)
Negative	4127 (86.5)	338 (96.9)	3789 (85.7)	3381 (84.8)	187 (96.4)	3194 (84.2)

*Out of 9470 girls and women surveyed, there were 8003 unique participants; 1467 took part in both Round 1 and Round 2 data collection.

experienced physical violence from a sexual partner. Lastly, of the 1467 females who participated in both data collection rounds, 25.0% (2 of 8) of girls and 8.2% (120 of 1459) of women experienced physical violence by a sexual partner.

Bivariate analysis: Factors associated with girls who experienced physical violence by a sexual partner in the last year

The risk of experiencing physical violence by a sexual partner was twice as high for girls who had no education or only some primary schooling (RR = 2.04, 95% confidence interval (CI) = 1.17, 3.56) compared to girls who had completed primary school or had higher levels of education. The risk was nearly 5 times as high for girls who were married or cohabiting (RR = 4.73, 95% CI = 2.43, 9.19) compared to being single, divorced widowed or separated, and nearly 5 times as high for girls who had 3 or more lifetime sexual partners (RR = 4.74, 95% CI = 2.23, 10.09) compared to 1. In addition, the risk of experiencing phys-

ical violence by a sexual partner was approximately twice as high for girls who reported their partners never used a condom (RR = 2.05, 95% CI = 1.23, 3.43), and would not say no to sex if partner had an STI (RR = 2.18, 95% CI = 1.29, 3.70). Finally, the risk was more than twice as high among girls who reported forced sex in last 12 months (RR = 2.52, 95% CI = 1.45, 4.38) and that their partner used alcohol at last sex and/or drugs in last 12 months (RR = 2.60, 95% CI = 1.36, 4.99). The number of girls who experienced physical violence by a sexual partner and self–reported being HIV positive (n = 3) were too few for analysis (**Table 2**).

Table 2. Factors associated with females who experienced physical violence by a sexual partner in the last 12 months by age; Gem, Kenya, 2011–2012 (Round 1) and 2013–2014 (Round 2)*

Variables	≤18 years				>18 years			
	Experienced physical violence by a sexual partner				Experienced physical violence by a sexual partner			
	Yes	No	RR (95% CI)	P	Yes	No	RR (95% CI)	P
Highest level of education:			–	0.01			–	0.02
None or some primary	36 (67.9)	281 (49.9)	2.04 (1.17, 3.56)		621 (57.9)	4200 (54.0)	1.15 (1.03, 1.29)	
Primary or above	17 (32.1)	282 (50.1)	Ref		451 (42.1)	3582 (46.0)	Ref	
Sources of income (cash):				0.2				<0.0001
None	11 (20.8)	164 (29.4)	Ref		107 (10.0)	1170 (15.0)	Ref	
Job/business	19 (35.9)	134 (24.0)	1.94 (0.95, 3.97)	0.07	786 (73.4)	5503 (70.8)	1.51 (1.25, 1.83)	<0.0001
Partner/family/other	23 (43.4)	260 (46.6)	1.32 (0.66, 2.64)	0.4	178 (16.6)	1105 (14.2)	1.65 (1.32, 2.07)	<0.0001
Marital status:				<0.0001				<0.0001
Single/Divorced/Widowed/ Separated/ Other	10 (18.9)	316 (56.1)	Ref		85 (7.9)	1194 (15.3)	Ref	
Married/Cohabiting	43 (81.1)	247 (43.9)	4.73 (2.43, 9.19)		987 (92.1)	6588 (84.7)	1.94 (1.57, 2.40)	
Number of pregnancies:				–				<0.0001
0–2	50 (96.2)	532 (95.9)	–		311 (29.0)	2086 (26.9)	1.29 (1.12, 1.49)	0.0004
3–4	2 (3.9)	10 (1.8)	–		351 (32.8)	1972 (25.4)	1.51 (1.31, 1.72)	<0.0001
≥5	0 (0.0)	13 (2.3)	Ref		409 (38.2)	3706 (47.7)	Ref	
Deliberately terminated a pregnancy:				0.5				<0.0001
Yes	5 (11.1)	18 (5.5)	0.65 (0.22, 1.99)		111 (10.8)	354 (4.8)	2.07 (1.74, 2.46)	
No	40 (88.9)	308 (94.5)	Ref		918 (89.2)	7035 (95.2)	Ref	
Lifetime No. of sexual partners:				0.0001				<0.0001
1	8 (15.7)	228 (41.1)	Ref		117 (11.4)	1155 (16.4)	Ref	
2	15 (29.4)	183 (33.0)	2.21 (0.96, 5.08)	0.06	273 (26.7)	2235 (31.7)	1.18 (0.96, 1.46)	0.1
≥3	28 (54.9)	144 (26.0)	4.74 (2.23, 10.09)	<0.0001	633 (61.9)	3664 (51.9)	1.60 (1.33, 1.95)	<0.0001
Ever used a condom:				0.006				0.02
Yes	24 (45.3)	364 (64.7)	Ref		376 (35.1)	2444 (31.5)	Ref	
No	29 (54.7)	199 (35.4)	2.05 (1.23, 3.43)		696 (64.9)	5327 (68.6)	0.87 (0.77, 0.98)	
If you knew your partner had an STI would say no to sex:				0.004				0.1
Yes	34 (65.4)	451 (81.6)	Ref		850 (79.8)	6324 (82.0)	Ref	
No	18 (34.6)	102 (18.4)	2.18 (1.29, 3.70)		215 (20.2)	1388 (18.0)	1.12 (0.98, 1.29)	
Forced sex in last 12 months:				0.001				<0.0001
Yes	15 (28.3)	68 (12.1)	2.52 (1.45, 4.38)		427 (39.9)	987 (12.7)	3.43 (3.07, 3.82)	
No	38 (71.7)	495 (87.9)	Ref		644 (60.1)	6789 (87.3)	Ref	
Partner used alcohol before last sex and/or drug use in last 12 months:				0.004				<0.0001
Yes	9 (17.3)	35 (6.6)	2.60 (1.36, 4.99)		3331 (32.3)	1009 (13.5)	2.49 (2.21, 2.81)	
No	42 (82.4)	496 (93.4)	Ref		694 (67.7)	6461 (86.5)	Ref	
Age at first sex:				0.70				<0.0001
≤15 years	16 (30.2)	183 (32.5)	Ref		512 (47.8)	4269 (52.9)	Ref	
>15 years	37 (69.8)	380 (67.5)	1.11 (0.63, 1.95)		560 (52.2)	3513 (49.1)	1.27 (1.14, 1.42)	
Self–reported HIV status:				–				
Positive	3 (6.4)	15 (3.0)	–		163 (16.5)	1069 (14.8)	1.12 (0.95, 1.31)	0.2
Negative	44 (93.6)	481 (97.0)	Ref		826 (83.5)	6157 (85.2)	Ref	
Round:				0.7				<0.0001
1	35 (66.0)	358 (63.6)	1.12 (0.65, 1.93)		704 (65.7)	4201 (54.0)	1.54 (1.38, 1.73)	
2	18 (34.0)	205 (36.4)	Ref		368 (34.3)	3581 (46.0)	Ref	

RR – risk ratio; 95% CI – confidence interval; Ref – reference value
*Percentage in each cell is computed using the total number of non–missing records as the denominator. In some cases the respondents had missing data for the covariates.

Table 3. Multivariable analysis – factors associated with experiencing physical violence by a sexual partner in the last 12 months by girls ≤18 years old, Gem, Kenya, 2011–2012 (Round 1) and 2013–2014 (Round 2)

Variables	aRR (95% CI)	P
Highest level of education:		0.01
None or some primary	1.98 (1.15, 3.41)	
Primary or above (Ref)	–	
Marital status:		<0.0001
Single/Divorced/Widowed/Separated (Ref)	–	
Married/Cohabiting	4.67 (2.42, 8.98)	
Forced sex last 12 months:		
Yes	2.39 (1.39, 4.14)	0.002
No (Ref)		

aRR – adjusted risk ratio; 95% CI – confidence interval, Ref – reference value

Multivariable analysis: Factors associated with girls who had experienced physical violence by a sexual partner in the last year

In the final multivariable analysis, the risk of physical violence by a sexual partner was nearly twice as high among girls who had no education or only some primary school (aRR = 1.98, 95% CI = 1.15, 3.41) compared to girls who had completed primary school or had higher levels of education, nearly 5 times as high among girls who were married or cohabiting (aRR = 4.67, 95% CI = 2.42, 8.98) compared to being single, divorced widowed or separated, and more than twice as high among girls who reported forced sex (aRR = 2.39, 95% CI = 1.39, 4.14) (**Table 3**).

Bivariate analysis: Factors associated with women who experienced physical violence by a sexual partner in the last year

The risk of experiencing physical violence by a sexual partner was 15% higher for women who had no education or only some primary school (RR = 1.15, 95% CI = 1.03, 1.29) compared to women who had completed primary school or had higher levels of education. The risk was nearly 50% higher for women who had income from a job or business (RR = 1.51, 95% CI = 1.25, 1.83) or partner/family (RR = 1.65, 95% CI = 1.32, 2.07) than no source of income, nearly twice as high for women who were married or cohabiting (RR = 1.94, 95% CI = 1.57, 2.40) compared to being single, divorced widowed or separated, and 29% higher for women who had 0–2 (RR = 1.29, 95% CI = 1.12, 1.49) and 51% higher for women who had 3–4 pregnancies (RR = 1.51, 95% CI = 1.31, 1.72) compared to those having 5 or more. In addition, the risk was twice as high for women who deliberately terminated a pregnancy (RR = 2.07, 95% CI = 1.74, 2.46), 60% higher for women who had 3 or more lifetime sexual partners (RR = 1.60, 95% CI = 1.33, 1.95) compared to 1, and over three times as high for women who reported forced sex in last 12 months (RR = 3.43, 95% CI = 3.07, 3.82). Finally, the risk of experiencing physical violence by a sexual partner was more than twice as high among women who reported that their partner used alcohol at last sex and/or drugs in the last 12 months (RR = 2.49, 95% CI = 2.21, 2.81), 27% higher among women who reported age at first sex was >15 years (RR = 1.27, 95% CI = 1.14, 1.42) and 13% lower among women who reported their partners had not ever used a condom (RR = 0.87, 95% CI = 0.77, 0.98). The risk of experiencing sexual violence by a partner was 54% higher among women in Round 1 (RR = 1.54, 95% CI = 1.38, 1.73) than in Round 2. There was no significant association between women who experienced physical violence by a sexual partner and self–report of HIV status (RR = 1.12, 95% CI = 0.95, 1.31) (**Table 2**).

Multivariable analysis: Factors associated with women who experienced physical violence by a sexual partner in the last year

In the final multivariable analysis, the risk of experiencing physical violence by a sexual partner was 16% higher among women who had no education or only some primary school (aRR = 1.16, 95% CI = 1.03, 1.30) compared to women who had completed primary school or had higher levels of education and twice as high for women who were married or cohabiting (aRR = 2.04, 95% CI = 1.60, 2.59) compared to being single, divorced widowed or separated. In addition, the risk was 34% higher among women who had ≥3 lifetime sexual partners (aRR = 1.34, 95% CI = 1.10, 1.63) compared to 1 and more than 2 times as high among women who reported forced sex in last 12 months (aRR = 2.53, 95% CI = 2.23, 2.88). The risk was 62% higher among women who had 0–2 pregnancies (aRR = 1.62, 95% CI = 1.39, 1.88) and 55% higher among women who had 3–4 pregnancies (aRR = 1.55, 95% CI = 1.36, 1.78) compared to those having 5 or more. Finally, the risk was nearly twice as high among women who reported that their partner used alcohol at last sex and/or drugs in the last 12 months (aRR = 1.82, 95% CI = 1.61, 2.08) and 45% higher among women who reported deliberately terminating a pregnancy (aRR = 1.45, 95% CI = 1.21, 1.74). The risk of experiencing physical violence by a sexual partner was 21% higher among women in Round 1 (aRR = 1.21, 95% CI = 1.07, 1.37) than in Round 2 (**Table 4**).

Table 4. Multivariable analysis – factors associated with being experiencing physical violence by a sexual partner in the last 12 months by women >18 years old in Gem, Kenya, 2011–2012 (Round 1) and 2013–2014 (Round 2)

Variables	aRR (95% CI)	P
Highest level of education:		0.01
None or some primary		
Primary or above (Ref)	1.16 (1.03, 1.30)	
Marital status:		<0.0001
Single/Divorced/Widowed/ Separated/Other (Ref)		
Married/Cohabiting	2.04 (1.60, 2.59)	
Lifetime No. of sexual partners:		0.002
1 (Ref)		
2	1.08 (0.87, 1.34)	0.50
≥3	1.34 (1.10, 1.63)	0.004
Forced sex last 12 months:		<0.0001
Yes	2.53 (2.23, 2.88)	
No (Ref)		
Number of pregnancies:		<0.0001
0–2	1.62 (1.39, 1.88)	<0.0001
3–4	1.55 (1.36, 1.78)	<0.0001
≥5 (Ref)		
Partner alcohol use at last sex and/or drug use in last 12 months:		<0.0001
Yes	1.82 (1.61, 2.08)	
No (Ref)		
Deliberately terminated a pregnancy:		
Yes	1.45 (1.21, 1.74)	<0.0001
No (Ref)		
Round:		
1	1.21 (1.07, 1.37)	0.002
2 (Ref)		

aRR – adjusted risk ratio; 95% CI – confidence interval

DISCUSSION

We found that nearly 12% of females in Gem, rural western Kenya, reported experiencing physical violence by a sexual partner in the last 12 months with the proportion significantly lower for girls (8.4%) than for women (11.8%). This is on the lower end of the range of reports of any physical violence (not just from a sexual partner) in the last year of between 3% and 52% of women in a global review [14] and lower than the 48.5% of Kenyan girls aged 13 to 17 years statistics [5]. Though, this is similar to the proportion (10%) reported in a study of pregnant Kenyan women seeking antenatal care [15]. While some study results have shown a relationship between IPV and HIV infection [6,16], like some other studies [15], we did not find an association. This may be due to different populations and cultures studied as well as the differences in study methods and variables measured [6].

Girls and women had three factors associated with experiencing physical violence by a sexual partner in common: low education, being married or cohabiting, and experiencing forced sex in the last 12 months. The risk of experiencing physical violence by a sexual partner was nearly twice as high for girls who had no education or only some primary school education compared to girls who had completed primary school or higher. For women the risk was lower, though nonetheless significant with women who had less education having a 15% greater risk of experiencing physical violence by a sexual partner than women with primary school education and above. Low education level has repeatedly been shown to be a risk factor for a host of adverse life events experienced by girls and women ranging from early sexual initiation [17], sexually transmitted diseases, abuse [18], HIV infection [19], mortality [20] and early marriage and pregnancy [17]. Relatedly, early marriage and pregnancy are important factors with regard to school drop–out [21]. Our study showed that physical violence by a sexual partner was nearly five times as high for girls and twice as high for women who were married or cohabiting. The fact that being married or cohabiting was strongly associated with physical violence by a sexual partner is not unexpected given the girl or woman's extended period of exposure to the sexual partner compared to those single, divorced or widowed. Finally, experiencing physical violence by a sexual partner was more than twice as high for girls and women who reported forced sex. It is noteworthy that forced sex is reported to be most often perpe-

trated by intimate partners [22]. In rural western Kenya, 41% of married girls aged 14 to 19 years reported forced sex by their spouses, while 45% reported physical abuse by their spouses [23]. While physical violence and forced sex are both types of intimate partner or domestic violence, we did not combined them as we were interested in correlates of physical violence. This separation of different types of intimate partner or domestic violence, is used by the United States Department of Justice [24]. Lack of education is interconnected with early marriage and forced sex. The 2004 Global Campaign for Education [25] report states: "it is general schooling that appears to make the most powerful impact on young people's sexual behavior and choices. A complete primary education leads to increased ability to evaluate, understand and apply facts; gains in confidence; and greater decision–making power in relationships" (p. 7). Other research has shown how multiple issues, such as food insecurity, illiteracy and poverty [26], interact with gender inequalities like forced sex [27].

Other factors associated with women who experienced physical violence by a sexual partner included alcohol and/or drug use by their partners and ever deliberately terminating a pregnancy. Data from the Kenya Demographic Health Survey identified Nyanza Province to have the highest rate of IPV with alcohol the strongest risk factor, specifically, a 2.5–higher rate of IPV if husbands are often drunk compared with non–drinking husbands [5]. In a meta–analysis of intimate partner violence and pregnancy termination, while experiencing IPV was not always a factor in wanting to end a pregnancy, the analysis suggested that violence can lead to a pregnancy (via coercion, rape, sexual assault, or contraceptive sabotage) which is then terminated [28].

Our study had several limitations. First, we only included questions on physical violence; we did not include questions on emotional or verbal abuse. Other studies have suggested an overlap between physical violence and psychological and sexual violence [24,29]. Second, we did not include a question on lifetime experience with physical violence from a sexual partner, only violence in the last 12 months. Third, we used questions that were not validated and relatedly, used only a single measure, not a violence scale. Fourth, HIV status was based on self–reported results and the lack of a relationship between physical violence by a sexual partner and HIV may have been affected by the fact that only those aware of their status were included in the analysis. Fifth our analysis was cross-sectional so the direction of associations cannot be determined. Sixth, the variables partner alcohol use at last sex and drug use in the last 12 months had small numbers so had to be combined. Seventh, some potentially important variables were not included in our analysis due to omission (eg, age at marriage or age at which cohabitation was initiated). Eighth, there was a potential for some causality between Round 1 and Round 2; interventions that occurred between the two survey rounds may have played a role. Finally, there may have been social desirability bias; our results may be low due to under reporting of physical abuse by a sexual partner.

In conclusion, low education level, being married or cohabiting, and reporting forced sex in the last 12 months were common factors associated with physical violence by a sexual partner for both girls and women in rural Kenya. Addressing violence against women is an urgent public health need [30]. To change the circumstances and conditions that can lead to violent behavior, we advocate focusing on keeping children in school at least through secondary school to reduce early marriage, to allow the development of characteristics such as dependability, judgement, motivation, and effort [31]. Areas of future research may include anti–violence interventions aimed at both girls and boys as a way to change cultural norms as well as wellness interventions aimed at families to support parental efforts to provide both formal education and wellness skills to their children that can also help in preventing early marriage. There is a convergence of global attention on the importance of social and structural factors impacting health with programs such as "Let Girls Learn", which builds on the USAID campaign for girls' education [32], "Together for Girls" which stimulates policies and programs to prevent sexual violence and provides supportive care and services for victims of sexual violence [33] and the DREAMS (Determined, Resilient, Empowered, AIDS–Free, Mentored and Safe) initiative, which aims to identify what is putting adolescent girls and young women at risk for HIV in 10 high burden countries in Africa [34] as well as multiple interventions [35,36]. For women and girls not in school, community structural and educational programs are needed, for instance a microfinance and training intervention, has been shown to reduce levels of intimate–partner violence [37], in addition to safe places to seek support. The World Health Organization suggests increasing access to post–primary, vocational and technical education for women to prevent IPV and improve overall health [38]. Indeed, Freudenberg and Ruglis [39] state "Education is one of the strongest predictors of health: the more schooling people have, the better their health is likely to be" (p. 1). This one intervention of keeping girls as well as boys in school through at least secondary school, with teachers trained in non–violent discipline [40] and tailored programs on anti–violence and personal, economic and sexual empowerment, should be a major focus of public health.

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Prevalence and phenotype of diabetes and prediabetes using fasting glucose vs HbA1c in a Caribbean population

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Background Both fasting plasma glucose (FPG) and HbA1c are recommended for the diagnosis of diabetes and prediabetes by the American Diabetes Association (ADA), and for diabetes by the World Health Organization. The ADA guidance is influential on clinical practice in many developing countries, including in the Caribbean and Latin America. We aimed to compare the prevalence and characteristics of individuals identified as having diabetes and prediabetes by FPG and HbA1c in a predominantly African ancestry Caribbean population.

Methods A representative population–based sample of 1234 adults (≥25 years of age) resident in Barbados was recruited. Standard methods with appropriate quality control were used to collect data on height, weight, blood pressure, fasting lipids and history of diagnosed diabetes, and to measure fasting glucose and HbA1c. Those with previously diagnosed diabetes (n = 192) were excluded from the analyses. Diabetes was defined as: FPG ≥7.0 mmol/L or HbA1c ≥6.5%; prediabetes as: FPG ≥5.6 to <7mmol/L or HbA1c ≥5.7 to <6.5%.

Results Complete data were available on 939 participants without previously diagnosed diabetes. The prevalence of undiagnosed diabetes was higher, but not significantly so, by HbA1c (4.9%, 95% CI 3.5, 6.8) vs FPG (3.5%, 2.4, 5.1). Overall 79 individuals had diabetes by either measure, but only 21 on both. The prevalence of prediabetes was higher by HbA1c compared to FPG: 41.7% (37.9, 45.6) vs 15.0% (12.8, 17.5). Overall 558 individuals had prediabetes by either measure, but only 107 on both. HbA1c, but not FPG, was significantly higher in women than men; and FPG, but not HbA1c, was significantly associated with raised triglycerides and low HDL cholesterol.

Conclusion The agreement between FPG and HbA1c defined hyperglycaemia is poor. In addition, there are some differences in the phenotype of those identified, and HbA1c gives a much higher prevalence of prediabetes. The routine use of HbA1c for screening and diagnosis in this population would have major implications for clinical and public health policies and resources. Given the lack of robust evidence, particularly for prediabetes, on whether intervention in the individuals identified would improve outcomes, this approach to screening and diagnosis cannot be currently recommended for this population.

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Globally there are estimated to be over 400 million people with diabetes, and of these 4 out of 5 live in low and middle income countries [1]. Diabetes is estimated to cause 5 million deaths per year, and is a major contributor to premature adult mortality [1]. A substantial proportion of people with Type 2 diabetes, which comprises approximately 90–95% of all persons with diabetes, are undiagnosed. This undiagnosed proportion can be as high as 80–90% in some of the poorest settings, such as in many of the countries of sub–Saharan Africa, and is typically around 20–30% in the world's richest countries, including most of those in Western Europe and North America [1].

In addition to individuals with diabetes, there are those with 'prediabetes' [2], also known as 'intermediate hyperglycaemia' [3]. These individuals have glucose levels that are above normal, but below the diagnostic threshold for diabetes. They are at increased risk of developing diabetes. There are three broad categories of prediabetes, and there is excellent evidence that among persons with one category (impaired glucose tolerance, which is based on the 2–hour post challenge result in an oral glucose tolerance test) the risk of developing diabetes can be substantially lowered through changes in diet and physical activity or the use of metformin [4].

There have been two major changes over the past 20 years to the diagnostic criteria for diabetes. In 1997 the American Diabetes Association (ADA) lowered the diagnostic cut–point for fasting plasma glucose from 7.8 mmol/L to 7 mmol/L, and recommended that fasting glucose becomes the main diagnostic test, rather than the more time–consuming and expensive oral glucose tolerance test, which includes collection of a fasting sample and a sample 2 hours after a 75g glucose load [5]. In 2009, the International Expert Committee, which included the ADA, recommended that the diagnosis could also be made using glycated haemoglobin, HbA1c, at a cut–point of 6.5% [6]. HbA1c reflects the exposure of red cells to glucose over their lifetime. In a person with normal haemoglobin the average lifespan of red cells is around 120 days [7], with the average age of red cells in circulation being in the order of 40–60 days [8]. HbA1c therefore can be interpreted as reflecting average glucose levels over this time. The major advantage of HbA1c is that it does not require the person to be fasting, but it has the disadvantage of being more expensive to measure, and that the result can be influenced by medical conditions that affect red cell turnover and/or produce abnormal haemoglobin [9]. The World Health Organization (WHO) followed in lowering the cut–point for fasting glucose and in accepting HbA1c as a diagnostic test in 1999 [10] and 2011 [9], respectively. However, unlike the ADA, WHO still emphasizes the desirability of continuing to use an oral glucose tolerance test as the gold standard for the diagnosis of diabetes, while acknowledging that the use of fasting glucose or HbA1c is more practical.

While the ADA and WHO diagnostic criteria for diabetes are identical, there are two major differences when it comes to the diagnosis of prediabetes (the ADA term) or intermediate hyperglycaemia (the WHO term). First, the ADA cut–point for prediabetes based on fasting plasma glucose (FPG) at 5.6 mmol/L [11] is lower than that recommended by WHO at 6.1 mmol/L [3]. Second, WHO does not believe that there is enough evidence to recommend using HbA1c to diagnose prediabetes [9], whereas the ADA does and defines it as an HbA1c level from 5.7 to <6.5% [11]. It is relevant to the aims of the work present here to note that the ADA recommends that all people with prediabetes, whatever the method of diagnosis, are entered into a structured diabetes prevention programme [11]. Thus, if changing the approach to diagnosis changes the numbers of individuals identified, this would have implications for health care resources.

The Caribbean is an ethnically and linguistically diverse region [12], that includes 18 English–speaking countries and territories that are part of the Caribbean Community (CARICOM) [13] and have some of the highest rates of diabetes and diabetes mortality in the Americas [1,14]. Barbados, where the work described here was undertaken, is part of the English–speaking Caribbean and a member of CARICOM. It is an independent country, with a population of around 280 000, over 90% of whom are of African ancestry [15]. While the diagnosis of diabetes in Barbados and other parts of the Caribbean to date has largely relied on fasting glucose, ADA guidance [11] is highly respected and influential, and the greater availability of accessible and good quality HbA1c assays means that it is increasingly being used.

In this paper we make use of a recently conducted population–based survey [16] in which all participants had both FPG and HbA1c measured. Our aim was to assess what difference, if any, would using HbA1c rather than FPG make to the identification of diabetes and prediabetes. Specifically, we sought to determine whether there would be a difference in prevalence of the conditions, the individuals identified and the characteristics of those individuals. Our aim was not to determine which measure better predicts complications or progression (that would require a very different type of study), but rather to determine what the local policy and resource implications might be of using one approach compared to the other. This, as far as we can determine, is the first study of its type conducted in the Caribbean.

METHODS

Overview of the study design and data collection

The Health of the Nation survey was a cross–sectional study of the Barbadian population aged 25 years and older, which aimed to provide estimates of the prevalence and social distribution of non–communicable diseases (NCDs) and their risk factors. Data were collected for 1234 participants on health conditions and behaviours, as well as sociodemographic information. Data collection took place between September 2011 and May 2013. The survey methods have been described in detail elsewhere [16] and are summarised here.

On behalf of the Ministry of Health of the Government of Barbados, and in collaboration with the Barbados Statistical Service, a multistage sampling process was used, with enumeration districts (EDs) selected with a probability proportional to their population size, households randomly selected within each ED, and a single eligible participant randomly selected from each household using the Kish method [17]. Staff from the Barbados Statistical Service made the first contact with each household and, if permission was given, the household details were passed on to members of the Health of the Nation survey team.

Data collection took place in participants' homes across two visits. At the first visit a standard questionnaire was completed by interview. Items collected included whether the participant had been told by a doctor that they had diabetes, and if so what type of treatment they were on. At this first visit, height, weight, waist and hip circumferences were recorded, and blood pressure was measured using an Omron HEM–705CP digital machine. Standard protocols were followed for all measurements, and data collection staff were trained and accredited in their use.

At the end of this first visit a second early morning visit was arranged for the collection of a venous blood sample, typically on the day after the first visit. The participant was instructed to fast overnight for at least 9 hours, drinking nothing other than water. The venous sample was collected into two tubes: a sodium fluoride tube and an EDTA tube. The sodium fluoride tube was placed immediately on wet ice, and the EDTA tube was placed in a cool box, which contained ice packs.

Assays of glucose, HbA1c and lipids

The sodium fluoride tube was kept on wet ice until its contents were analysed for plasma glucose later that morning. This analysis was undertaken at the Barbados Reference Laboratory using the glucose hexokinase method on Roche Cobas 6000 (Roche Diagnostics, Mannheim, Germany).

The sample in the EDTA tube was used for HbA1c and lipid analyses. All analyses were conducted during the same morning as the sample collection. Lipids (total cholesterol, HDL cholesterol and triglycerides) were analysed using a Reflotron biochemical analyser (Roche Diagnostics, Mannheim, Germany). HbA1c was analysed using a DCA 2000 analyser (Siemens Health Care Diagnostics, Munich, Germany), a method certified by NGSP and directly traceable to the DCCT reference [18] and which is not affected by common haemoglobin variants such as HbC and HbS [19]. Manufacturers' recommended quality control procedures for all biochemical assays were followed throughout.

The Reflotron and DCA 2000 analyser were used as they provide assay methods that are practical, affordable, widely used in surveys and known to be of good quality compared to laboratory standard methods [20–23]. However, we wished to be able to align the HbA1c and lipid results with those from the Barbados Reference Laboratory, an internationally accredited laboratory (with the College of American Pathologists – CAP). This was achieved by analysing duplicate samples, 56 for HbA1c and 50 for lipids. For HbA1c, this was done at the time of venepuncture by collecting blood into two separate EDTA tubes, with one tube going to the reference laboratory, where HbA1c was measured using high performance liquid chromatography (HPLC). For the lipids, 50 plasma aliquots, which had been stored at minus 80°C, were assayed in the reference laboratory for total, HDL and LDL cholesterol and triglycerides on a Roche Cobas 6000 analyzer.

Details of the comparison between the values of HbA1c and the lipids assessed by the two different assay methods are given in the supplementary material. There were small but statistically significant differences between the results from the survey assay methods and those in the Barbados Reference Laboratory. As would be expected, there was inter–individual variation in the size of the differences. These are expressed as the standard deviation of the differences [24] and show that 95% of the differences for the lipids lay

within 0.2 and 0.7 mmol/L (Table S1 in **Online Supplementary Document**) of the mean, and for HbA1c within 1% (Table S1 in **Online Supplementary Document**). As described in the supplement, simple linear regression equations were applied to the survey results to align them with reference laboratory values.

Statistical analyses

Data were analysed using Stata statistical software (version 13, StataCorp, College Station, Texas). Weights were applied to account for the sampling design, non–response at the ED level, and to match the age and sex distribution of the Barbadian population according to the 2010 census [15]. As described elsewhere, compared with the official population, provided by the 2010 Barbados Population and Housing Census, the survey generally under–sampled young adults and oversampled the elderly, and more women than men took part. These discrepancies were addressed by the weighting scheme, full details of which are available on–line in the publication by Howitt et al [16].

Categories of hyperglycaemia were defined according to the criteria of the ADA [11] and the WHO [3,9]. Diabetes was defined, according to both ADA and WHO criteria, as FPG ≥7.0 mmol/L or HbA1c ≥6.5%. Prediabetes according to ADA criteria was defined as FPG ≥5.6 to <7 mmol/L or HbA1c ≥5.7 to <6.5%. Prediabetes (impaired fasting glucose) according to WHO criteria was defined as FPG of ≥6.1 to <7 mmol/L.

Those with previously diagnosed diabetes (n = 192) were excluded from the analyses in which the classification and characteristics according to FPG and HbA1c values were compared. Agreement was investigated in unweighted analyses in which categories based on FPG and HbA1c were cross–tabulated. Unweighted kappa statistics, using the Kappa command in Stata, were calculated.

The characteristics of individuals with ADA–defined hyperglycaemia were investigated as follows. First, differences (with 95% confidence intervals) in means and proportions between individuals with hyperglycaemia (ie, above the prediabetes cut–point) and normoglycaemia were examined. This was performed separately for the HbA1c and FPG defined categories. Age and sex were compared, plus anthropometric and biological variables commonly associated with hyperglycaemia [25]: body mass index, waist circumference, systolic and diastolic blood pressure, HDL cholesterol and triglycerides. The association of normo/hyperglycaemia with hypertension, as a binary variable (yes/no), was also examined, in order to allow for the fact that some individuals may have normal blood pressure readings because they are on treatment. Hypertension was defined as being on [or using prescribed] medication for hypertension and/or systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg. Second, logistic regression was undertaken to identify which characteristics were independently associated with hyperglycaemia. A backward step selection process was used, starting with all the independent variables in the model and removing the least significantly associated variable at each step. This was halted when all variables in the model were associated with a *P* value of at least <0.05. All the analyses were undertaken using the survey module in Stata, in order to apply appropriate weights given the sampling design, non–response and age and sex distribution of the Barbados population (as described above). Model specification was evaluated using the link test and goodness of fit using the 'estat gof' command [26].

Ethical considerations

Written informed consent was obtained from all participants. The study was approved by the Research Ethics Committee of the University of the West Indies, Cave Hill and the Barbados Ministry of Health. All persons in the study found to have abnormal results, including abnormal HbA1c or FPG, were informed and advised to seek medical advice and further investigation as needed.

RESULTS

There was a total of 1234 respondents (470 men and 764 women). Out of 2277 eligible households contacted by the Barbados Statistical Service, 1646 (72.3%) agreed to having their details passed on to the Health of the Nation survey; from these, 1234 (75.0%) individuals participated in the study (see Howitt et al. for full details [16]).

Diagnosed diabetes was reported by 192 participants, 11.4% (95% confidence interval (CI) 8.3, 15.5) of men and 15.8% (95% CI 13.1, 18.8) of women (**Table 1**). Of the 1042 without a previous diagnosis of diabetes, complete data on fasting glucose and HbA1c were available on 939 (90%). In these individuals, the prevalence of previously undiagnosed diabetes ranges from 3.5% (95% CI 2.4, 5.1) (FPG criterion in

Table 1. Prevalence of categories of diabetes and prediabetes in Barbadian adults (25 years and over)*

	Men (n = 430)	Women (n = 701)	All (n = 1131)
Diagnosed diabetes (n = 192):			
On hypoglycaemic medication	9.2 (6.6, 12.8)	13.8 (11.4, 16.7)	11.7 (9.8, 13.8)
Not on medication	2.1 (1.1, 4.1)	1.9 (1.0, 3.7)	2.0 (1.2, 3.3)
All	11.4 (8.3, 15.5)	15.8 (13.1, 18.8)	13.8 (11.7, 16.2)
Undiagnosed diabetes:†			
FPG ≥7.0 mmol/L	3.3 (2.0, 5.5)	3.7 (2.2, 6.3)	3.5 (2.4, 5.1)
HBA1c ≥6.5%	3.9 (2.3, 6.5)	5.7 (3.9, 8.3)	4.9 (3.5, 6.8)
On either of above	5.7 (3.9, 8.3)	7.3 (5.0, 10.4)	6.5 (4.9, 8.6)
Prediabetes (WHO criteria):			
FPG ≥6.1 to <7 mmol/L	5.5 (3.5, 8.5)	4.4 (2.8, 6.7)	4.9 (3.5,6.9)
Prediabetes (ADA criteria):†			
FPG ≥5.6 to <7 mmol/L	16.7 (12.9, 21.2)	13.6 (10.6, 17.2)	15.0 (12.8, 17.5)
HBA1c ≥5.7 to <6.5%	39.7 (33.8, 46.0)	43.4 (39.8, 47.2)	41.7 (37.9, 45.6)
On either of above	42.2 (35.9, 48.8)	45.8 (42.2, 49.4)	44.1 (40.5, 47.9)

FPG – fasting plasma glucose, HBA1c – haemoglobin A1c, ADA – American Diabetes Association
*Figures are percentages (95% confidence intervals), and are weighted for sampling design, non–response and the age structure of the Barbados adult population.
†See **Table 2** for numbers of individuals (unweighted) by category.

men and women) to 7.3% (95% CI 5.0, 10.4) (FPG and/or HbA1c criterion in men and women). The prevalence of previously undiagnosed diabetes is higher by the HbA1c criterion compared to the FPG in both women and men; and higher in women compared to men by both the HbA1c and FPG criteria. However, the confidence intervals are wide and overlapping.

The prevalence of prediabetes differs markedly by the three different sets of criteria (**Table 1**). The lowest prevalence is for the WHO FPG criterion, with an overall prevalence in men and women of 4.9% (95% CI 3.5, 6.9). Applying the ADA FPG criterion triples the prevalence, to 15.0% (95% CI 12.8, 17.5). Applying the ADA HbA1c criterion gives more than double the ADA FPG prevalence, at 41.7% (95% CI 37.9, 45.6). Defining prediabetes based on either FPG or HbA1c gives a prevalence of 44.1% (95% CI 40.5, 47.9).

The agreement between diabetes and prediabetes according to ADA FPG vs HbA1c criteria is poor, reflected by low kappa values (**Table 2**). For example, there are 43 individuals with previously undiagnosed diabetes based on FPG, and 57 based on HbA1c, but only 21 on both (kappa 0.39, 95% CI 0.32, 0.45). With prediabetes there are 170 based on FPG, 495 on the HbA1c, and only 107 on both (kappa 0.14, 95% CI 0.10, 0.19).

Table 2. Agreement between categories of diabetes and prediabetes based on fasting plasma glucose (FPG) and HbA1c criteria*

	FPG		
HbA1c:	**Not diabetes**	**Diabetes**	**Total**
Not diabetes	860	22	882
Diabetes	36	21	57
Total	896	43	939
Kappa (95% CI)	0.39 (0.32, 0.45)		
	ADA Categories based on FPG		
ADA categories based on HbA1c	**Normal**	**Prediabetes**	**Diabetes**	**Total**
Normal	342	37	8	387
Prediabetes	374	107	14	495
Diabetes	10	26	21	57
Total	726	170	43	939
Kappa (95% CI)	0.14 (0.10, 0.19)			

CI – confidence interval, FPG – fasting plasma glucose, HBA1c – haemoglobin A1c, ADA – American Diabetes Association
*Figures are numbers of study participants, and kappa statistics (95% confidence intervals).

Anthropometric and biological characteristics of those without a previous diagnosis of diabetes are summarised in **Table 3**. There are notable differences between men and women, with women having a significantly (based on the lack of overlap between 95% confidence intervals) higher body mass index, HbA1c, total and HDL cholesterol, but similar fasting glucose, and lower triglycerides and lower mean systolic blood pressure. A higher proportion of women than men are on treatment for hypertension. The prevalence of obesity (BMI ≥30 kg/m²) is 43.5% (95% CI 39.1, 48.0) in women and 23.2% (95% CI 18.4, 28.8) in men.

Selected characteristics of those with ADA–defined hyperglycaemia compared to those with normoglycaemia by FPG and HbA1c criteria are shown in **Table 4**. Older age, higher body mass index, waist circumference and blood

Table 3. Characteristics of those without previously diagnosed diabetes, and with complete fasting glucose and HbA1c data*

	MEN	WOMEN	ALL
Age in years (n, column %):			
25–44	139 (38.5)	252 (43.6)	391 (41.6)
45–64	155 (42.9)	237 (41.0)	392 (41.8)
65+	67 (18.6)	89 (15.4)	156 (16.6)
All	361 (100.0)	578 (100.0)	939 (100.0)
Glucose & HbA1c:			
Mean fasting glucose (mmol/L)	5.2 (5.1, 5.3)	5.2 (5.1, 5.4)	5.2 (5.2, 5.3)
Mean HbA1c (%)	5.7 (5.6, 5.7)	5.8 (5.7, 5.9)	5.7 (5.7, 5.8)
Other:			
Anthropometry			
Mean BMI (kg/m^2)	26.4 (25.7, 27.1)	29.8 (29.1, 30.5)	28.2 (27.8, 28.6)
Mean waist circumference (cm)	90.1 (88.1, 92.0)	92.6 (91.2, 94.1)	92.1 (91.1, 93.1)
Blood pressure:			
Mean sBP (mmHg)	131.0 (129.1, 133.0)	126.5 (124.5, 128.6)	128.7 (127.3, 130.1)
Mean dBP (mmHg)	77.8 (76.3, 79.3)	76.8 (75.7, 77.8)	77.3 (76.4, 78.2)
% On treatment for hypertension	14.1 (10.9, 18.1)	25.3 (20.4, 30.8)	19.9 (16.7, 23.6)
Lipids:			
Mean total cholesterol (mmol/L)	4.6 (4.5, 4.7)	4.9 (4.8, 4.9)	4.7 (4.7, 4.8)
Mean HDL cholesterol(mmol/L)	1.28 (1.25, 1.31)	1.40 (1.38, 1.43)	1.34 (1.32, 1.36)
Mean triglycerides (mmol/L)	0.96 (0.92, 1.00)	0.88 (0.85, 0.92)	0.92 (0.90, 0.94)

HBA1c – haemoglobin A1c, BMI – body mass index, sBP – systolic blood pressure, dBP – diastolic blood pressure, HDL – high density lipoprotein
*103 individuals of the 1042 without previously diagnosed diabetes had missing fasting glucose and/or HbA1c values. All figures, with the exception of the numbers by age group, are weighted for the sampling design, non–response, and the age structure of the Barbados adult population.

Table 4. Comparison of selected characteristics between groups with normal and raised fasting glucose or HbA1c based on ADA criteria*

	NORMAL	RAISED	ABSOLUTE DIFFERENCE (95% CI)
Fasting glucose:			
Age (years)	45.2 (0.8)	53.7 (1.5)	8.5 (5.5, 11.4)
Female sex (%)	52.7%	50.1%	−2.8 (−12.3, 6.7)
BMI (kg/m^2)	27.5 (0.4)	30.1 (0.6)	2.5 (1.0, 4.0)
Waist (cm)	89.8 (0.8)	97.0 (1.2)	7.0 (3.9, 10.2)
sBP (mmHg)	126.6 (0.7)	135.9 (1.9)	9.2 (5.3, 13.0)
dBP (mmHg)	76.4 (0.5)	80.3 (1.1)	4.1 (1.8, 6.3)
Hypertension (%)†	28.4	56.8	28.3 (19.0, 37.6)
HDL cholesterol (mmol/L)	1.36 (0.01)	1.29 (0.02)	−0.07 (−0.12, −0.02)
Triglycerides (mmol/L)	0.97 (0.02)	1.17 (0.06)	0.20 (0.07, 0.34)
HbA1c:			
Age (years)	41.3 (0.8)	51.9 (0.9)	10.9 (8.6, 13.2)
Female sex (%)	46.8%	56.6%	9.6 (2.5, 16.6)
BMI (kg/m^2)	26.5 (0.4)	29.5 (0.4)	3.0 (1.7, 4.2)
Waist (cm)	87.0 (1.0)	94.9 (0.8)	7.7 (4.9, 10.5)
sBP (mmHg)	124.8 (1.0)	131.8 (0.9)	7.4 (4.8, 10.1)
dBP (mmHg)	75.9 (0.8)	78.4 (0.6)	2.8 (1.0, 4.7)
Hypertension (%)†	22.2	44.9	22.7 (15.3, 30.0)
HDL cholesterol (mmol/L)	1.34 (0.02)	1.34 (0.02)	0.00 (−0.05, 00.1)
Triglycerides (mmol/L)	0.96 (0.03)	1.05 (0.03)	0.09 (0.00, 00.2)

HBA1c – haemoglobin A1c, BMI – body mass index, sBP – systolic blood pressure, dBP – diastolic blood pressure, HDL – high density lipoprotein
*Figures are means (standard error) unless otherwise indicated.
†On BP lowering medication and/or blood pressure ≥140/90. See text for details.

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Table 5. Results of logistic regression to identify independent associations between hyperglycaemia and the characteristics in **Table 4**

	Odds Ratio	95% CIs
Fasting glucose:		
Age (years)	1.03	1.01, 1.04
Waist (cm)	1.03	1.01, 1.05
Hypertension (Y/N)	2.03	1.25, 3.30
Triglycerides (mmol/L)	1.46	1.07, 2.00
HbA1c:		
Age (years)	1.05	1.04, 1.07
Female sex	1.40	1.03, 1.91
Waist (cm)	1.04	1.02, 1.06
HbA1c (model with sex specific "high waist"*):		
Age (years)	1.06	1.04, 1.07
Female sex	1.25	0.94, 1.66
High waist (Y/N)	2.32	1.50, 3.58

HBA1c – haemoglobin A1c
*≥94 cm in women; ≥102 cm in men.

pressure are all related to both FPG and HbA1c categories of hyperglycaemia. Higher triglyceride, and lower HDL cholesterol levels are associated with FPG, but not HbA1c, defined hyperglycaemia. Female sex is associated with HbA1c, but not FPG, defined hyperglycaemia.

Backward step logistic regression, as described in the methods section and starting with all the variables shown in **Table 4** was undertaken to identify factors independently associated with FPG and HbA1c categories of hyperglycaemia. The FPG category was independently associated with age, waist circumference, hypertension and triglycerides (**Table 5**). The HbA1c category was associated with age, waist circumference and female sex, but not blood pressure, HDL cholesterol or triglycerides. In further analysis, waist circumference was entered into the model for HbA1c as a binary variable using sex specific cut–points (94 cm for women, 102 cm for men [27]). As shown in **Table 5**, this had the effect of reducing the association with female sex (odds ratio (OR) 1.25, 95% CI 0.94, 1.66).

DISCUSSION

In the first study of its type in the Caribbean, we compared the prevalence and agreement of diabetes and prediabetes as defined by FPG and HbA1c. We found that HbA1c gave a higher prevalence of both diabetes (non–significant) and prediabetes. Applying the ADA criteria, the prevalence of prediabetes was more than twice as high based on HbA1c compared to fasting glucose. The agreement between the two methods of classification was poor. There were also differences in the factors associated with HbA1c and FPG-defined hyperglycaemia. HbA1c, but not FPG, defined hyperglycaemia was associated with female sex. Raised FPG, but not HbA1c, defined hyperglycaemia was associated with raised triglycerides and hypertension. At a population level, therefore, there are important differences in terms of prevalence and the characteristics of the individuals identified.

While both HbA1c and FPG are recommended by the ADA and WHO for the diagnosis of diabetes, and by the ADA for the diagnosis of prediabetes, it is unclear whether one should be preferred over the other. Analyses of cross–sectional data from nine studies across five countries found that both FPG and HbA1c at the currently recommended diagnostic cut–points for diabetes were strongly associated with an increased risk of diabetic retinopathy, whereas the 2–hour glucose from an oral glucose tolerance test was not [28]. Prediabetes, whether defined by HbA1c or FPG, is associated with an increased risk of developing diabetes [29]. However, it does not appear that one test is better than the other at predicting harder adverse outcomes, such as death or incident cardiovascular disease. For example, neither adds much to the prediction of cardiovascular events when other established cardiovascular risk factors are taken into account [30].

It is also unclear, given the currently available evidence, whether the lifestyle and pharmacological interventions that have been shown to substantially reduce the incidence of diabetes in those with impaired glucose tolerance [4], which requires an oral glucose tolerance test for diagnosis, are also effective in those with prediabetes based on FPG or HbA1c. It seems a reasonable assumption that they would be, and indeed guidance is based on this assumption [11]. However, hard evidence is lacking, and what does exist suggests that in the case of impaired fasting glucose these interventions may be either ineffective or much less effective [31,32]. Comparable studies targeting prediabetes based on HbA1c do not exist [29].

Other studies have also investigated differences in the prevalence of diabetes and prediabetes by different measures of glycaemia, whether HbA1c, FPG, or the use of an oral glucose tolerance test. A pooled analysis to investigate the impact on diabetes prevalence, based on 63 health examination surveys, found differences in prevalence (both higher and lower), with similar prevalences in only a minority (15%) [33]. Differences in agreement between studies were significantly, but weakly, related to population differences in body mass index and gross domestic product [33]. For example, in a pooled regression analysis, the prevalence of diabetes by HbA1c, while controlling for the prevalence by FPG, was positively related with age, mean body mass index, and gross domestic project [33].

Studies reporting differences in the prevalence of prediabetes by FPG and HbA1c have also found differences in both directions. In the Canadian Health Measures Survey, for example, differences in the prevalence of prediabetes in adults based on ADA criteria by FPG and HbA1c are similar to what we describe here: 13% using FPG vs 33% with HbA1c [34]. In the United States (US) NHANES study, by contrast, the prevalences of prediabetes were almost the reverse: 28.7% with FPG and 12.4% with HbA1c [35]. The reasons for these differences are not clear based on the published data. Neither study presented a comparison by sex, nor compared the characteristics of those with differently defined prediabetes. The higher prevalence of obesity in the US (30–33%) compared to Canada (20–22%) [36] is not obviously related to these differences. Interestingly, in a relatively small study (n = 216) of predominantly male (mean age 37 years) African migrants to the US, the prevalence of hyperglycaemia (taking the figures from **Table 2** in the paper) [37] using ADA criteria was 13% by FPG and 35% by HbA1c, similar to what we report in our study here.

It is also relevant to our findings to note that some analyses, in particular based on data from the US NHANES study, have described higher levels of HbA1c in black compared to white participants ('black' and 'white' being the terms used in the paper) independent of differences in fasting and post challenge glucose [38]. Similarly, in the Atherosclerosis Risk in Communities Study, HbA1c levels were higher in black compared to white participants independent of fasting glucose level [39]. The American Diabetes Prevention Program (conducted in adults with impaired glucose tolerance) also reported differences by ethnicity in average HbA1c levels, with higher levels in black compared to white participants, and these were independent of differences in obesity, fasting and post challenge glucose, and insulin resistance [40]. It may be, therefore, that relationships between measures of glucose (including fasting and post challenge) and HbA1c differ by ethnic group, with a higher HbA1c level in people of black African origin compared to people of white European origin [41,42]. The reasons for such differences remain unclear and include potential racial/ethnic differences in susceptibility to glycation of haemoglobin [41,42], and underlying average glucose concentrations being higher in African descent populations (and not properly accounted for by adjusting for fasting and post challenge glucose).

One little mentioned but possible contributory factor to population differences in HbA1c levels is iron deficiency. This may increase red cell life and thus HbA1c levels [43,44]. It is possible that iron deficiency anaemia in women of child–bearing age contributes to the higher HbA1c levels in women found in our study. Unfortunately, haemoglobin was not measured in the survey, but WHO estimates for the prevalence of iron deficiency anaemia in Barbados suggest that around one in five to one in four women aged 15–49 are anaemic [45]. The potential effect of iron deficiency anaemia on HbA1c levels requires further evaluation. Another, possibly more important, contributory factor to higher HbA1c levels in women compared to men in Barbados is the higher prevalence of obesity, particularly abdominal obesity. Controlling for abdominal obesity, defined using sex–specific cut–points, reduced to non–significant the association of HbA1c defined hyperglycaemia with female sex.

Before drawing conclusions on the implications of the findings reported here, we should acknowledge both the strengths and limitations of the study. A strength is that this is a representative population–based study. Standardised methods were used to collect all data, most importantly to measure FPG and HbA1c. The method of HbA1c measurement used is approved by the NGSP [18] and widely used, and in addition we aligned these values to those from the only reference laboratory in Barbados that uses the gold standard approach of HPLC. Limitations of the study include that it was a relatively small study population, and thus lacks precision to properly investigate some areas of interest, including differences in diabetes prevalence by FPG or HbA1c. In addition, it was an epidemiological study using epidemiological definitions of prediabetes and undiagnosed diabetes; ie, our definitions are based on a single measurement, whereas in clinical practice, and in the absence of clear symptoms, a confirmatory diagnostic test should always be performed [3,11]. Finally, it is worth noting that the kappa statistic to assess agreement between categories based on FPG and HbA1c requires careful interpretation. Kappa values are influenced by the prevalence of the different categories, and when the prevalence is very different (such as the prevalence of diabetes vs no diabetes), Kappa may provide an overly negative summary of the agreement [46]. We recommend therefore that the Kappa values are only used and interpreted alongside the actual cross–tabulated data (**Table 2**). Despite these limitations, our findings demonstrate marked differences between FPG and HbA1c in the identification of hyperglycaemia in the adult population of Barbados.

In conclusion, current guidance recommends the use of both FPG and HbA1c for the diagnosis of diabetes and prediabetes. This study has shown that according to ADA guidance around 44% of the adult population of Barbados has prediabetes, with a further 6.5% having previously undiagnosed diabetes. When

previously diagnosed diabetes is added, roughly two out of three (64%) adults are classified as having either diabetes or prediabetes and thus the majority of the adult population would be recommended for clinical intervention [11]. By contrast, if WHO diagnostic guidance is followed then roughly one in four adults (25%) has either diabetes or prediabetes. In very well–resourced settings it might be considered prudent to measure both FPG and HbA1c and manage individuals accordingly, as is recommended [11]. However, in less well–resourced settings, such as in Barbados and most of the Caribbean, our findings indicate that the increasing use of HbA1c to diagnose diabetes and prediabetes could have major implications: for human and financial resources; clinical practice and public health policies; and for health systems that are already struggling to cope with the high and increasing burden of chronic diseases. In addition, there is limited evidence to support whether one approach is better than the other for identifying individuals who will benefit from treatment. In short, the currently available guidance is particularly unhelpful, and potentially damaging (if it leads to less effective use of scarce resources), for situations in which resources are limited. We propose therefore that a pragmatic approach, guided by the currently available evidence, is to use FPG as the diagnostic test for both diabetes and prediabetes and to restrict the label of 'prediabetes' to the narrow range recommended by WHO. Expansion of the prediabetes category, whether by adopting the broader ADA FPG range or using HbA1c criteria, should be contingent upon clear evidence that cost–effective interventions to improve outcomes are available [29].

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Determinants of Integrated Management of Childhood Illness (IMCI) non–severe pneumonia classification and care in Malawi health facilities: Analysis of a national facility census

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Background Research shows inadequate Integrated Management of Childhood Illness (IMCI)–pneumonia care in various low–income settings but evidence is largely from small–scale studies with limited evidence of patient–, provider– and facility–levels determinants of IMCI non–severe pneumonia classification and its management.

Methods The Malawi Service Provision Assessment 2013–2014 included 3149 outpatients aged 2–59 months with completed observations, interviews and re–examinations. Mixed–effects logistic regression models quantified the influence of patient–, provider and facility–level determinants on having IMCI non–severe pneumonia and its management in observed consultations.

Findings Among 3149 eligible outpatients, 590 (18.7%) had IMCI non–severe pneumonia classification in re–examination. 228 (38.7%) classified cases received first–line antibiotics and 159 (26.9%) received no antibiotics. 18.6% with cough or difficult breathing had 60–second respiratory rates counted during consultations, and conducting this assessment was significantly associated with IMCI training ever received (odds ratio (OR) = 2.37, 95% confidence interval (CI): 1.29–4.31) and negative rapid diagnostic test results (OR = 3.21, 95% CI: 1.45–7.13). Older children had lower odds of assessments than infants (OR = 48–59 months: 0.35, 95% CI: 0.16–0.75). Children presenting with any of the following complaints also had reduced odds of assessment: fever, diarrhea, skin problem or any danger sign. First–line antibiotic treatment for classified cases was significantly associated with high temperatures (OR = 3.26, 95% CI: 1.24–8.55) while older children had reduced odds of first–line treatment compared to infants (OR = 48–59 months: 0.29, 95% CI: 0.10–0.83). RDT–confirmed malaria was a significant predictor of no antibiotic receipt for IMCI non–severe pneumonia (OR = 10.65, 95% CI: 2.39–47.36).

Conclusions IMCI non–severe pneumonia care was sub–optimal in Malawi health facilities in 2013–2014 with inadequate assessments and prescribing practices that must be addressed to reduce this leading cause of mortality. Child's symptoms and age, malaria diagnosis and provider training were primary influences on assessment and treatment practices. Current evidence could be used to better target IMCI training and support to improve pneumonia care for sick children in Malawi facilities.

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Despite the enormous progress in child survival over the past two decades, approximately six million children under five years still die each year globally [1]. These deaths largely occur during the neonatal period or are due to infectious causes, such as pneumonia [2]. Indeed, pneumonia remains a leading cause of child mortality accounting for nearly one million under–five deaths annually. Early and effective treatment of childhood pneumonia is therefore a cornerstone of child survival programs [3].

Since the 1990s, WHO and UNICEF have promoted the Integrated Management of Childhood Illness (IMCI) strategy in low– and middle–income countries to effectively manage pneumonia and other common causes of child morbidity and mortality in an integrated manner [4]. While IMCI has great potential to improve health worker performance and quality care for sick children [5], poor implementation in routine practice has been documented in various settings over the past few decades [6,7]. This includes inadequate care for the IMCI–pneumonia algorithm in particular, which has been demonstrated in Malawi [8,9] although a more recent study from rural Malawi suggested stronger IMCI–pneumonia performance among service providers [10].

Yet this evidence is largely derived from small–scale studies in limited facility contexts without examination of determinants of IMCI–pneumonia classification or its case management. A national facility census, or Service Provision Assessment (SPA), was conducted in Malawi in 2013–2014 that included observed sick child consultations and re–examinations [11]. While an analysis of overall correct IMCI–pneumonia care is not possible using this facility census given limited observation and re–examination protocols (see Methods), it does provide a unique opportunity to identify determinants of having an IMCI non–severe pneumonia episode, such as child's age or symptoms [12,13]. It also allows for a wide ranging assessment of patient–, provider– and facility–level predictors for conducting select assessments (60–second respiratory rate count) and prescribing first–line treatment to classified cases. Such evidence could help target IMCI training and support going forward in order to improve quality pneumonia care across Malawi health facilities.

METHODS

Study setting

Malawi is a low–income country in sub–Saharan Africa with an estimated population of 17 million [14]. Malawi's under–five mortality rate declined from 242 deaths per 1000 live births in 1990 to 64 in 2015 [1], which achieved the Millennium Development Goal for child mortality. This significant reduction has been attributed to scaling–up interventions effective against the leading causes of child death, reducing child undernutrition and mother–to–child HIV transmission as well as improving quality childbirth care [15]. Prior to the Malawi Service Provision Assessment (SPA) in 2013–2014, IMCI guidelines were last updated in 2013 to reflect test–based malaria case management and wide–scale IMCI in–service training was previously implemented in 2009. Nationwide deployment of malaria rapid diagnostic tests (RDT) was initiated in July 2011 accompanied by training in RDT safety and use along with basic information on managing RDT–negative cases [16].

The Malawi health system generally includes both government facilities and publicly–supported facilities managed by the Christian Health Association of Malawi (CHAM) [16]. The three facility levels include health centers, district hospitals and regional hospitals. Health centers are the lowest level and deliver primary health care services that are generally led by a medical assistant or nurse midwife technician. District hospitals are referral facilities at the next level that provide in–patient care, laboratory diagnostics and maternity care that are generally led by medical doctors and clinical officers. Regional or central hospitals are the highest level that are generally research and teaching institutions that provide specialized medical care. Community treatment services are also available for sick children but were not included in this facility–based assessment.

Survey methods

The Malawi Service Provision Assessment (SPA) was conducted in June 2013–February 2014 by the Ministry of Health and The DHS Program, which includes facility and laboratory audits, observed consultations with limited re–examination, patient exit interviews and health worker interviews. Survey methods are described elsewhere including procedures for obtaining ethical approval and participant consent [11].

Briefly, Malawi SPA 2013–2014 was designed as a census of all formal public and private facilities in the country to include 977 facilities out of 1060 on the Ministry of Health master facility list. Non–response

was due to refusal (3%), closure (2%), inaccessibility (2%) or other issue (1%). At each facility, outpatients were systematically selected for observation based on the expected patient load for sick child curative services on the interview date in order to yield no more than 15 observations per facility. Outpatients were eligible to participate if they were less than five years old and presented with an illness complaint that was not an exclusive injury or non–disease condition. Children aged 2–59 months attending an observed outpatient consultation were included in this study if consent for the observed consultation, exit interview and re–examination were obtained. A total of 3149 observations met these criteria and were included in the analysis (**Figure 1**). A median of 3 observations were conducted at each facility.

During each observed sick child consultation, an observer was present to silently record whether certain IMCI assessments or examinations were completed, such as felt the child for fever or body hotness, counted breathing for 60 seconds or checked skin turgor for dehydration. However, there is no recording of assessment quality nor were all IMCI assessments included in the observer checklist, notably it was not recorded if the provider checked for chest in–drawing or asked about illness duration. After each consultation, the observer asked the provider to report all diagnoses/classifications and treatments prescribed to the sick child. A limited re–examination protocol was conducted during the exit interview and included measuring temperature, checking anemia symptoms and counting respiratory rates for 60 seconds if cough or difficult breathing (CDB) was reported. Both the observed consultation and re–examination was conducted by clinicians, nurses or nurse midwives trained in these specific protocols. For these reasons, it was not possible to directly assess correct pneumonia case management by comparing observed practices with 'gold standard' re–examination since neither the observation or re–examination provided complete information for such analyses. Nevertheless, the large number of facilities audited and broad data collection scope provide an opportunity to examine a wide–range of determinants for having a IMCI non–severe pneumonia episode, performing certain assessments and prescribing antibiotics for classified cases.

Classification of IMCI non–severe pneumonia

IMCI non–severe pneumonia was defined in this study according to 2013 Malawi IMCI guidelines [17]. It was based on re–examination of the child as having a cough and difficult breathing (CDB) complaint and rapid breathing of 50 or more breaths per minute (2 up to 12 months) or 40 or more breaths per minute (12 to 59 months). IMCI severe pneumonia is classified based on chest in–drawing with or without fast breathing. However, chest in–drawing assessment was not part of re–examination or recorded as
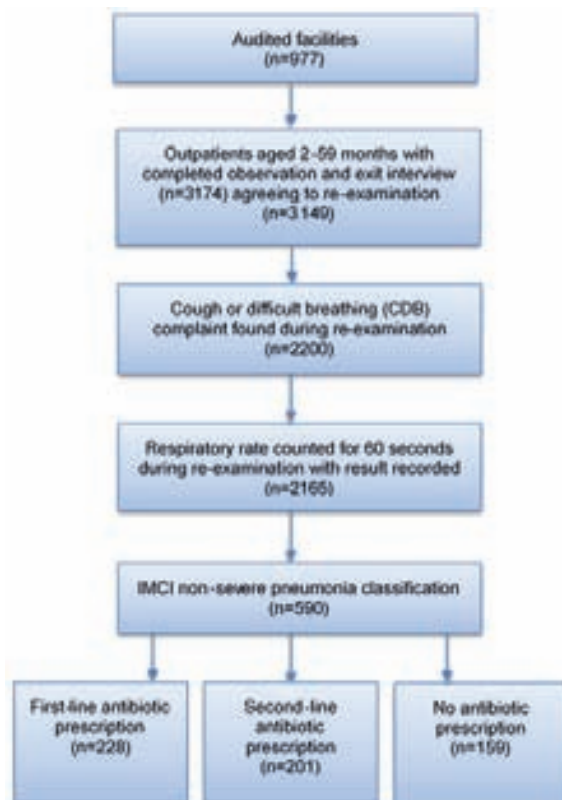
Figure 1. Study sample. Frequencies were weighted to account for the unequal probabilities of selection due to differing client volumes on the interview date. IMCI non–severe pneumonia classification is defined as cough or difficult breathing complaint and a respiratory rate of 50 breaths or more per minute (2 up to 12 months) or 40 breaths or more per minute (12 months up to 5 years) recorded during re–examination. First–line antibiotic prescription refers to benzyl penicillin injection or amoxicillin (capsule or syrup). Second–line antibiotic prescription refers to cotrimoxazole (syrup or tablet) or other antibiotic (injection, syrup or capsule). Antibiotic treatment totals sum to 588 observations (not 590) due to missing values.

done in the observed consultation. For this reason, our analysis focuses on IMCI non–severe pneumonia since a raised respiratory rate *at least* indicates non–severe classification. In 2014, IMCI guidelines were updated to define non–severe pneumonia as fast breathing and/or chest in–drawing but this revision occurred after survey implementation and is not used in this paper [18].

Assessment of IMCI non–severe pneumonia

IMCI non–severe pneumonia assessment was defined as a 60–second respiratory rate count observed and recorded during the consultation. This analysis was based on the subset of outpatients aged 2–59 months with CDB complaint reported in the exit interview.

Treatment of IMCI non–severe pneumonia

IMCI non–severe pneumonia treatment was derived from provider reports of treatments prescribed to the sick child after the observation. First–line antibiotic treatment included benzyl penicillin injection or amoxicillin (capsule or syrup) since it was not possible to differentiate severe and non–severe cases in this data set. Second–line antibiotic treatment included cotrimoxazole (syrup or tablet) or other antibiotic (injection, syrup or capsule). Hierarchical coding assigned the most appropriate prescription to the observation if multiple drugs were prescribed. This analysis was based on the subset of outpatients aged 2–59 months with IMCI non–severe pneumonia that attended a facility with amoxicillin available on the interview date. Only 13 IMCI non–severe pneumonia cases (unweighted) were observed in facilities without amoxicillin and these observations were removed from this analysis.

Explanatory variables

Patient–, provider and facility–level variables with potential to affect IMCI–pneumonia classification and care were explored in these analyses [8–10,19–25]. Patient–level variables included child's sex and age (2–11, 12–23, 24–35, 36–47, 48–59 months), caregiver's age (Under 20, 20–29, 30–39, 40 or more years), caregiver's education (none, primary or at least secondary attendance), RDT conducted prior to or during the initial consultation according to provider reports, and if so, reported RDT results (positive or negative), child's temperature (37.5 or less, 37.6–38.9 or 39.0–40.8) recorded in re–examination, illness duration (0–1, 2–4, 5 or more days), consultation start hour (7–10 am, 11–2 pm, 3–5 pm) recorded in the observation, reported wait time (under 10, 11–30, 31–60, 60 or more minutes), first or follow–up visit for the current illness, and symptom complaints (fever, diarrhea, ear problem, eye problem, skin problem or any danger sign). Any danger sign includes vomits everything, convulsions, lethargy or inability to eat, drink or breastfeed. Patient–level variables were reported by the caregiver during the exit interview unless otherwise noted.

Provider–level variables included job qualification (doctor, medical assistant, nurse or other provider) and year qualification received (before 2000, 2001–2009, 2010 to present), provider sex, supervisor or in–charge status, IMCI in–service training ever received or not and recent supervisory visit (none, within past 3 months, over 3 months ago). Provider–level variables were reported during the provider interview.

Facility–level variables included facility type (hospital or other), managing authority (government or CHAM/other private), total staff doctors (0, 1, 2+ doctors), routine general user fees or not, routine management meetings reportedly occur or not, region (north, central, south), location (urban, rural), timer available, amoxicillin or any antibiotic available, as well as malaria risk (infection prevalence) values for 2013–2014 linked to data sets through geocoded facility locations and transmission season estimates derived from facility locations and interview date [26,27]. Facility–level variables were recorded during the facility audit unless otherwise noted.

Missing values

Observations with missing values were removed from analyses using listwise deletion. For the IMCI non–severe pneumonia classification analysis, 158 (5%) observations were dropped that had missing values for at least one explanatory variable. For the assessment and treatment analyses, 65 (3%) and 9 (2%) observations were removed respectively.

Data analyses

Mixed–effects logistic regression models quantified the influence of explanatory variables on the binary outcomes of interest. Variables were included as categorical fixed effects nested within facility identifiers

and normal distribution of the random effects was assumed. Bivariate analyses were initially conducted for each variable to estimate crude odds ratios separately for each of the outcomes. Variables found to be statistically significant at the 0.1 level in bivariate analyses were subsequently included in final models to obtain adjusted odds ratios. Variance inflation factors were used to detect multi–collinearity among variables prior to inclusion in final models. Given the importance of child's age in model outputs, we tested for an interaction between child's age and IMCI training on the assessment and treatment outcomes in final models. Results were stratified to examine effect differences across age groups (2–11, 12–23, 24–35, 36–47, 48–59 months). Point estimates were calculated using weights to account for unequal probabilities of selection due to differing client volumes at facilities on the interview date. Standard error estimation accounted for clustering of client observations within facilities. The level of statistical significance was set to 0.05. Stata 13.1 (Stata Corp., College Station, TX) was used for analyses.

RESULTS

Among 3149 eligible outpatients aged 2–59 months, 590 (18.7%) were classified with IMCI non–severe pneumonia in re–examination (Table 1). Among these classified cases, 228 (38.7%) received benzyl pen-

Table 1. Characteristics of outpatients aged 2–59 months with IMCI non–severe pneumonia, Malawi health facilities, 2013–2014*

		Outpatients aged 2–59 months (No.)	IMCI non–severe pneumonia (No.)	Percent IMCI non–severe pneumonia (95% CI)
Total		**3149**	**590**	**18.7 (16.6–21.1)**
Fever complaint	Yes	2110	397	18.8 (16.4–21.5)
	No	962	164	17.0 (13.5–21.3)
Diarrhea complaint	Yes	899	166	18.5 (15.2–22.3)
	No	2249	423	18.7 (16.3–21.5)
Danger sign complaint	Yes	1481	283	19.1 (16.3–22.4)
	No	1669	307	18.4 (15.7–21.4)
RDT result	Positive	378	78	20.6 (15.1–27.5)
	Negative	653	151	23.2 (18.8–28.1)
Temperature (Celsius)	37.5 or less	2436	410	16.8 (14.5–19.3)
	37.6–38.9	595	144	24.3 (19.9–29.2)
	39.0–40.8	99	30	30.6 (21.7–41.3)
Child's age (months)	2–11	1124	166	14.7 (11.5–18.7)
	12–23	912	261	28.6 (24.6–33.0)
	24–35	540	88	16.2 (12.6–20.7)
	36–47	317	39	12.2 (8.4–17.3)
	48–59	257	37	14.5 (9.6–21.2)
Illness duration (days)	0–1	726	135	18.6 (15.0–22.7)
	2–4	1992	363	18.2 (15.7–21.0)
	5 or more	420	92	22.0 (17.0–28.0)
Malaria endemicity (PfPR$_{2–10}$)	Under 0.20	2367	448	18.9 (16.4–21.6)
	0.20–0.39	782	142	18.2 (14.4–22.7)
Transmission season	Peak	428	68	15.9 (12.3–20.3)
	Off–peak	2721	522	19.2 (16.8–21.8)
Residence	Urban	1007	170	16.8 (12.4–22.5)
	Rural	2142	420	19.6 (17.5–22.0)
Region	North	463	68	14.7 (11.5–18.7)
	Central	1583	317	20.0 (17.2–23.1)
	South	1103	205	18.4 (14.6–23.4)
Any antibiotic observed	Yes	3142	589	18.6 (16.5–20.9)
	No	3	<1	25.0 (—)
Amoxicillin observed	Yes	3094	580	18.7 (16.6–21.1)
	No	52	10	18.8 (9.9–33.0)
Facility type	Hospital (central, district, rural, other)	1136	200	17.6 (13.1–23.2)
	Other facility type	2014	390	19.4 (17.4–21.5)
Managing authority	Government	2404	454	18.9 (16.3–21.8)
	CHAM or other private ownership	745	136	18.2 (15.2–21.8)

IMCI – Integrated Management of Childhood Illness, CI – confidence interval, RDT – rapid diagnostic test, PfPR – *Plasmodium falciparum* parasite rate, CHAM – Christian Health Association of Malawi

*Outpatients aged 2–59 months with completed observations, exit interviews and re–examinations were included. IMCI non–severe pneumonia classification was identified in re–examination based on CDB complaint and a 60–second respiratory rate count of 50 or more breaths per minute (2 up to 12 months) and 40 or more breaths per minute (12 months to 5 years). Frequencies and cross–tabulations were weighted to account for the unequal probabilities of selection due to differing client volumes on the interview date.

icillin injection or amoxicillin, 157 (26.6%) received cotrimoxazole, 44 (7.5%) received other antibiotics and 159 (26.9%) received no antibiotic (**Figure 1**). Among 2271 outpatients aged 2–59 months with CDB complaints reported in the exit interview, 422 (18.6%) had a 60–second respiratory rate counted in the consultation (**Online Supplementary Document**).

IMCI non–severe pneumonia classification

Table 2 indicates a significant association between child's age, raised temperature and illness duration on having IMCI non–severe pneumonia classification. Compared to infants, there was nearly three times higher odds of having this classification among 12–23 months (odds ratio (OR) = 2.87, 95% confidence interval (CI): 2.17–3.78) while there was no statistical difference with older age groups. Outpatients with a moderate or high temperature had 1.59 (95% CI: 1.21–2.09) and 2.38 (95% CI: 1.41–4.04) times higher odds of receiving this classification respectively than those with no or low temperature. Compared to a short illness duration (0–1 day), outpatients reporting illness lasting 5+ days had 1.57 (95% CI: 1.08–2.27) times higher odds of having IMCI non–severe pneumonia.

Count respiratory rates for 60 seconds

Table 3 shows the significance of child's age, symptoms, IMCI in–service training, provider qualification, region and reported wait time on the odds of receiving a 60–second respiratory rate count to assess IMCI non–severe pneumonia. There was a significant and consistent decline in assessment odds with increas-

Table 2. Determinants of IMCI non–severe pneumonia classification in outpatients aged 2–59 months, Malawi health facilities, 2013–2014*

			Adjusted OR	95% CI	P
Patient	Fever complaint	No	1.00		
		Yes	1.07	0.83–1.38	0.616
	Diarrhea complaint	No	1.00		
		Yes	0.80	0.62–1.03	0.090
	Danger sign complaint	No	1.00		
		Yes	1.09	0.87–1.37	0.438
	Temperature (Celsius)	37.5 or less	1.00		
		37.6–38.9	1.59	1.21–2.09	0.001
		39.0–40.8	2.38	1.41–4.04	0.001
	Child's age (months)	2–11	1.00		
		12–23	2.87	2.17–3.78	<0.001
		24–35	1.25	0.89–1.76	0.192
		36–47	0.94	0.62–1.45	0.794
		48–59	1.05	0.67–1.66	0.824
	Illness duration (days)	0–1	1.00		
		2–4	1.08	0.82–1.43	0.571
		5 or more	1.57	1.08–2.27	0.016
Facility	Malaria endemicity (PfPR$_{2-10}$)	Less than 0.20	1.00		
		0.20–0.39	0.76	0.52–1.10	0.148
	Transmission season	Peak	1.00		
		Off–peak	0.89	0.61–1.29	0.538
	Residence	Urban	1.00		
		Rural	1.26	0.87–1.82	0.225
	Region	North	1.00		
		Central	1.48	0.98–2.24	0.061
		South	0.91	0.61–1.35	0.623
	Facility type	Hospital (central, district, rural, other)	1.00		
		Other facility type	1.06	0.71–1.59	0.769
	Managing authority	Government	1.00		
		CHAM or other private ownership	0.93	0.69–1.26	0.654

IMCI – Integrated Management of Childhood Illness, CI – confidence interval, OR – odds ratio, PfPR – Plasmodium falciparum parasite rate, CHAM – Christian Health Association of Malawi

*Variables presented in this table were significant (*P* < 0.1) in bivariate analyses and were then included simultaneously in the final model to obtain adjusted odds ratios. Mixed–effects logistic regression models quantified the influence of the above variables on receiving IMCI non–severe pneumonia classification (or not) adjusted for data clustering.

Table 3. Determinants of taking a 60–second respiratory rate count in outpatients aged 2–59 months with cough or difficult breathing complaints, Malawi health facilities, 2013–2014*

			Adjusted OR	**95% CI**	**P**
Patient	Fever complaint	No	1.00		
		Yes	0.62	0.43–0.95	0.018
	Diarrhea complaint	No	1.00		
		Yes	0.61	0.43–1.01	0.023
	Skin problem complaint	No	1.00		
		Yes	0.21	0.07–0.64	0.006
	Any danger sign complaint	No	1.00		
		Yes	0.70	0.49–1.02	0.052
	Child's age (months)	2–11	1.00		
		12–23	0.62	0.49–0.95	0.030
		24–35	0.38	0.22–0.65	<0.001
		36–47	0.53	0.27–1.05	0.070
		48–59	0.35	0.16–0.75	0.007
	Caregiver's age (years)	11–19	1.00		
		20–29	0.64	0.35–1.14	0.125
		30–39	1.20	0.61–2.27	0.627
		40 or older	0.33	0.10–1.14	0.080
	Wait time (minutes)	10 or less	1.00		
		11–30	0.42	0.22–0.81	0.009
		31–59	0.74	0.41–1.32	0.303
		60 or more	1.00	0.56–1.75	0.955
	RDT results†	Positive	1.00		
		Negative	3.21	1.45–7.13	0.001
Facility	Malaria endemicity (PfPR$_{2-10}$)	Less than 0.20	1.00		
		0.20–0.39	1.25	0.60–2.61	0.630
	Region	North	1.00		
		Central	1.15	0.50–2.60	0.749
		South	0.31	0.13–0.71	0.006
	Doctors (total on staff)	0	1.00		
		1	1.40	0.38–5.49	0.593
		2 or more	0.33	0.09–1.17	0.085
	IMCI guidelines available	No	1.00		
		Yes	1.19	0.64–2.32	0.546
Provider	Qualification	Doctor	1.00		
		Medical assistant	0.78	0.37–1.80	0.607
		Nurse or other provider	0.33	0.12–1.01	0.051
	Supervisor or in–charge	No	1.00		
		Yes	1.29	0.68–2.46	0.425
	Qualification received (year)	Before 2000	1.00		
		2000–2009	1.15	0.56–2.33	0.713
		2010 to present	0.69	0.30–1.60	0.394
	IMCI in–service training (ever received)	No	1.00		
		Yes	2.37	1.29–4.31	0.006

CI – confidence interval, OR – odds ratio, RDT – rapid diagnostic test, PfPR – Plasmodium falciparum parasite rate, CHAM – Christian Health Association of Malawi, IMCI – Integrated Management of Childhood Illness

*Table S1 in **Online Supplementary Document** presents descriptive statistics for outpatients aged 2–59 months with CDB complaints reported in exit interviews (n=2271). CI refers to confidence interval. Variables presented in this table were significant (P<0.1) in bivariate analyses and were then included simultaneously in the final model to obtain adjusted odds ratios. Mixed–effects logistic regression models quantified the influence of the above variables on counting respiratory rates for 60 s (or not) adjusted for data clustering.

†RDT results is based on a subset analysis of outpatients with CDB complaints and reported RDT results (n=692).

ing age of the child. Compared to infants, the odds of receiving a 60–second respiratory rate count declined by 38% for 12–23 months (OR=0.62, 95% CI: 0.49–0.95), by 62% for 24–35 months (OR=0.38, 95% CI: 0.22–0.65), by 47% for 36–47 months (OR=0.53, 95% CI: 0.27–1.05) and by 65% for 48–59 months (OR=0.35, 95% CI: 0.16–0.75).

Reporting other symptoms with CDB complaint significantly reduced the odds of having a 60–second respiratory rate counted in the consultation. Assessment odds declined by 38% if fever was reported (OR=0.62, 95% CI: 0.43–0.95) compared to not reported, by 39% if diarrhea was reported (OR=0.61,

95% CI: 0.43–1.01), by 79% for reported skin problems (OR = 0.21, 95% CI: 0.07–0.64), and by 30% if any danger sign was reported although the latter was not a statistically significant reduction (OR = 0.70, 95% CI: 0.49–1.02).

Outpatients attended by providers that ever received IMCI in–service training had 2.37 times higher odds of receiving a 60–second respiratory rate count (95% CI: 1.29–4.31) than those seen by providers without such training. Compared to doctors, clients attended by nurses, midwives or other lower–level providers had reduced assessment odds (OR = 0.33, 95% CI: 0.12–1.01) although there was no significant difference with medical assistants. Attendance at facilities in the South region was associated with significantly lower assessment odds (OR = 0.31, 95% CI: 0.13–0.71) than in the North region. In a subset analysis of outpatients with CDB complaints and reported RDT results (n = 692), RDT–negative cases had 3.21 times higher assessment odds than outpatients with RDT–confirmed malaria (95% CI: 1.45–7.13) in the adjusted analysis.

There was also evidence of an interaction between categorical variables child's age and IMCI training (p–values ranged from 0.006 to 0.813) on the assessment outcome. To further explore this result, the final model was stratified by age groupings. Outpatients aged 12–23 months (OR = 9.56, 95% CI: 3.03–30.18) and 48–59 months (OR = 261.97, 95% CI: 1.46–47281.50) that visited providers ever receiving IMCI in–service training had significantly higher assessment odds than outpatients seen by providers with no such training although effect sizes should be interpreted with caution due to few observations and positive outcomes (Table 4). There was a negligible difference between those visiting trained and untrained providers in other age groups. There was also limited overlap in confidence intervals of the adjusted odds ratios for 2–11 and 12 to 23–month–olds suggesting a difference across these age groups in the effect of training on assessment odds. Stratified models for the treatment outcome showed no significant difference in IMCI training across age groupings (data not shown).

Antibiotic prescriptions

Figure 2 depicts antibiotic prescriptions for IMCI non–severe pneumonia cases across different age groups. Nearly half (45.9%) of infants with IMCI non–severe pneumonia received first–line antibiotics and this proportion consistently declined with older ages to a low of 18.3% among 48 to 59–month–olds. In contrast, second–line antibiotics (cotrimoxazole or other antibiotic) were more often prescribed to older children with 50.5% of 48 to 59–month–olds incorrectly treated compared to 26.2% of infants. The proportion of outpatients receiving no antibiotic for IMCI non–severe pneumonia ranged from 22.0% among 24 to 35–month–olds to 31.2% among those 48–59 months old.

First–line antibiotic treatment of classified cases was significantly associated with younger ages, high temperatures and more staff doctors (Table 5). Compared to infants, odds of first–line treatment declined by 67% for ages 36–47 months (OR = 0.33, 95% CI: 0.12–0.88) and by 71% for ages 48–59 months (OR = 0.29, 95% CI: 0.10–0.83) while there was no statistical difference with other age groups. Outpatients with high temperatures (39.0°C or more) had 3.26 times higher odds of receiving first–line antibiotics than those with low or no temperature (95% CI: 1.24–8.55). Children with IMCI non–severe pneumonia attending facilities with two or more staff doctors had 2.90 times higher odds of receiving first–line antibiotic treatment than those visiting facilities with no staff doctors (95% CI: 1.22–6.88).

Table 4. Effect of IMCI training on counting respiratory rates for 60 s across age groupings, Malawi health facilities, 2013–2014*

	IMCI in–service training (ever received or not)	Adjusted OR	95% CI	P
2–11 months	No	1.00		
	Yes	1.50	0.70–3.24	0.301
12–23 months	No	1.00		
	Yes	9.56	3.03–30.18	<0.001
24–35 months	No	1.00		
	Yes	2.06	0.60–7.07	0.250
36–47 months	No	1.00		
	Yes	2.04	0.35–11.85	0.429
48–59 months	No	1.00		
	Yes	261.97	1.46–47 281.50	0.036

IMCI – Integrated Management of Childhood Illness, CI – confidence interval, OR – odds ratio

*Mixed–effects logistic regression models quantified the influence of IMCI in–service training on counting respiratory rates for 60 s (or not) across each age group adjusted for variables listed in Table 3 and data clustering. Results for the children aged 48–59 months should be interpreted with caution due to few observations and positive outcomes.
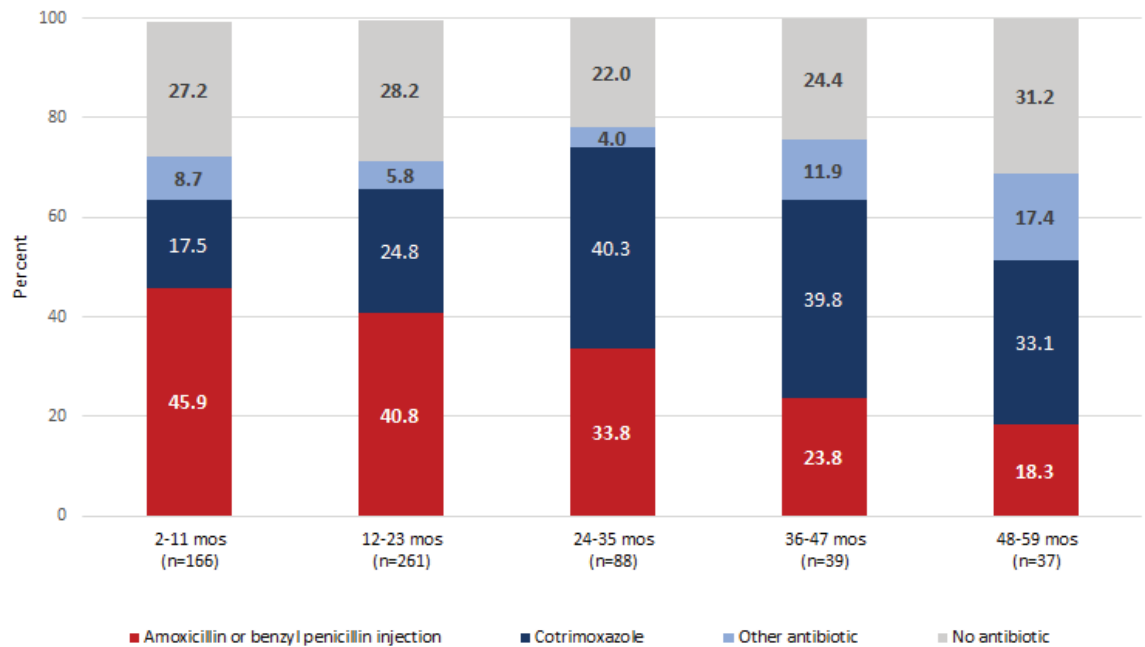
Figure 2. Antibiotic prescriptions for IMCI non–severe pneumonia by age groups, Malawi health facilities, 2013–2014. Frequencies were weighted to account for the unequal probabilities of selection due to differing client volumes on the interview date.

Table 5. Determinants of first–line antibiotic treatment for IMCI non–severe pneumonia in outpatients aged 2–59 month, Malawi health facilities, 2013–2014*

			Adjusted OR	95% CI	P
Patient	Temperature (Celsius)	37.5 or less	1.00		
		37.6–38.9	1.17	0.69–1.97	0.569
		39.0–40.8	3.26	1.24–8.55	0.016
	Child's age (months)	2–11	1.00		
		12–23	0.83	0.48–1.43	0.502
		24–35	0.62	0.31–1.25	0.183
		36–47	0.33	0.12–0.88	0.027
		48–59	0.29	0.10–0.83	0.021
Facility	Transmission season	Peak	1.00		
		Off–peak	0.61	0.29–1.27	0.187
	Region	North	1.00		
		Central	1.87	0.88–3.97	0.103
		South	0.94	0.45–1.98	0.875
	Total staff doctors	0	1.00		
		1	0.58	0.18–1.89	0.264
		2 or more	2.90	1.22–6.88	0.016

IMCI – Integrated Management of Childhood Illness, OR – odds ratio, CI – confidence interval

*Table S2 in **Online Supplementary Document** presents descriptive statistics for outpatients aged 2–59 mo with IMCI non–severe pneumonia classification receiving first–line antibiotic treatment (n=590). CI refers to confidence interval. Variables presented in this table were significant ($P<0.1$) in bivariate analyses and were subsequently included simultaneously in the final model to obtain adjusted odds ratios. Mixed–effects logistic regression models quantified the influence of variables on first–line antibiotic treatment (or not) adjusted for data clustering. A total of 13 observations (unweighted) with IMCI non–severe pneumonia attended facilities without amoxicillin available on the interview date and these observations were removed from this analysis. Analyses for no antibiotic prescription for IMCI non–severe pneumonia found only diarrhea significantly associated with no treatment in the bivariate analyses (crude OR=1.80, 95% CI: 1.08–3.01). In the subset analysis among sick child clients aged 2–59 mo with IMCI non–severe pneumonia and RDT results (n=216), RDT–positive cases had 10.65 times higher odds of no antibiotic prescription than RDT–negative cases (adjusted OR=10.65, 95% CI: 2.39–47.36).

In contrast, those with IMCI non–severe pneumonia who also presented with a diarrhea complaint had significantly higher odds of no antibiotic treatment in the bivariate analysis (OR=1.80, 95% CI: 1.08–3.01) while no other significant bivariate associations were identified. Among classified cases with RDT results (n=216), RDT–positive cases had significantly higher odds of no antibiotic receipt than RDT–negative cases (95% CI: 2.39–47.36) although the effect size should be interpreted with caution due to few observations and positive outcomes.

DISCUSSION

Overall, there was sub–optimal IMCI–pneumonia care in Malawi health facilities in 2013–2014 in terms of completed assessments and antibiotic prescriptions for non–severe cases. Child's symptoms and age, malaria diagnosis and provider training were main influences on assessment and treatment practices in this study, which could help inform IMCI training and support to improve pneumonia care for sick children.

In this study, IMCI non–severe pneumonia classification was significantly associated with raised temperature, child's age and illness duration that are biologically plausible results and consistent with findings from other research [12,13,28]. While previous studies have shown strong correlations between measured or reported fever and IMCI–pneumonia classification, our findings indicate that nearly 1 in 5 (17%) children without a measured fever (37.5°C or less) had IMCI non–severe pneumonia classification in re–examination. This result is higher than expected and may potentially reflect rapid breathing over–diagnosis in re–examination since misclassification can occur even among trained providers [29].

Few patients with CDB complaints had a 60–second respiratory rate counted in the observation, which is consistent with research from Malawi and other settings [5,6,8]. Assessment for IMCI–pneumonia occurred less often if other symptoms were reported (fever, diarrhea, skin problems or any danger sign) or for RDT–confirmed malaria cases as well as among older children, those living in the South region or outpatients attending providers without IMCI in–service training or with lower job qualifications. Other research in both African and Asian settings has shown that malaria diagnosis or reporting other symptom complaints reduced correct IMCI–pneumonia management [23,30,31]. It is critical that IMCI training reinforce the importance of assessing outpatients for multiple conditions given symptom overlap and common co–morbidities particularly among the sickest children at highest risk of death [32].

Some evidence also suggests that IMCI training may improve health worker skills reinforcing current findings although the long–term impact of training programs on performance has been debated [33,34]. Our results also indicate poor assessment performance among lower–level providers that has been shown in other research from Malawi, and enhanced IMCI support may need to specifically target these providers [23]. Poorer IMCI–pneumonia assessment in the South region compared to the North has not been previously reported to our knowledge but is consistent with greater child mortality reductions found in the North than the South region in 2000–2013 [15].

There was a significant and consistent decline in counting respiratory rates with increasing age of the child that has been shown in other settings [35], and could reflect more clinical probing of infants given higher mortality rates in this age group. There may also be higher suspicion of bacterial infections in infants that could also drive higher assessment rates as suggested in qualitative research [24]. Yet while children aged 12–23 months are less often assessed for IMCI–pneumonia than infants, our findings indicate higher rates of IMCI non–severe pneumonia classification in this age group. This disconnect should be addressed through enhanced IMCI training and support, particularly since our stratified analysis suggests IMCI training may potentially have greater effect on raising assessment rates in this older age group. Beyond the clinical setting, the identified under–classification and under–treatment of pneumonia cases may also be informative for regional and global burden of disease estimates more broadly [2].

Common mistreatment of IMCI non–severe pneumonia cases was also found in this analysis. Few (39%) cases were prescribed first–line antibiotics while 27% classified cases received no antibiotic prescription despite attendance at facilities with available amoxicillin. Poor antibiotic targeting for IMCI non–severe pneumonia closely follows poor assessments for antibiotic need as previously discussed. First–line antibiotic prescription for classified cases was associated with raised temperature, child's age and total staff doctors while receipt of no antibiotic prescription was associated with diarrhea complaint and RDT–confirmed malaria. Importantly, there was a significant and consistent decline in first–line treatment with increasing age of the child that also occurred with IMCI–pneumonia assessment. In addition, among older children with IMCI–pneumonia, second–line treatment (cotrimoxazole or other antibiotic) was more often prescribed even with amoxicillin available in the facility. This could suggest prioritization of first–line treatment for younger children at higher risk of dying or where there may be greater suspicion of bacterial infection. Higher temperatures also seemed to decrease the likelihood of pneumonia assessment while

increasing the potential for antibiotic prescriptions suggesting sicker children are prioritized for treatment regardless of assessed need.

Results should be viewed in light of some data limitations. First, health workers may perform better during observations and there could be worse IMCI–pneumonia care in routine practice although this effect could wane over repeated observations [36,37]. Second, the observation protocol does not record all assessments in the IMCI pneumonia algorithm such as looking for wheeze, chest in–drawing or stridor that are needed to classify severe pneumonia. The quality of the assessment is also not recorded such as whether breathing rates were correctly counted in a calm child for 60 seconds while using a timer. Third, the re–examination protocol was limited to a 60–second respiratory rate count, measured temperature and recorded signs of anemia given time and staff constraints. Other signs of severe pneumonia were not assessed such as chest in–drawing or hypoxia nor were there assessments of general danger signs indicating severe disease requiring urgent attention. For these reasons, this study could not assess correct IMCI–pneumonia management overall including differentiation among severe from non–severe cases, nor the full IMCI protocol more broadly. Also, we did not assess the new IMCI pneumonia algorithm defining non–severe pneumonia as fast breathing and/or chest in–drawing. It is possible that chest in–drawing could improve pneumonia classification although some children with IMCI–pneumonia will not present with in–drawing making current results of continued importance. It is also possible that chest in–drawing assessment could be similarly associated with child's age or other symptoms as found in this study. Fourth, rapid breathing can be difficult to assess even by trained providers leading to misclassification in either direction [29]. Finally, the IMCI algorithm was designed to include deliberate over–treatment of targeted conditions and recent studies have found IMCI–pneumonia is commonly classified in children who do not have x–ray confirmed disease [38,39]. Many outpatients with IMCI–pneumonia in this analysis likely do not need antibiotics although IMCI guidelines specify antibiotic treatment for presence of cough and fast breathing. The current lack of diagnostics to identify those in need of antibiotics will sustain continued misdirected treatment practices.

CONCLUSIONS

Based on a national facility census including 3149 observed sick children aged 2–59 months, study findings indicate sub–optimal care for IMCI non–severe pneumonia in terms of completed assessments and antibiotic prescriptions. Few classified cases received first–line antibiotics and counting respiratory rates was not often conducted. Results reinforce the primary importance of child's symptoms and age, malaria diagnosis as well as provider qualification and training on IMCI–pneumonia care in Malawi health facilities. Enhanced training and support is needed improve IMCI implementation particularly for the pneumonia algorithm, and current results suggest ways to better target these programs in the future. Greater focus on improved IMCI pneumonia care is urgently needed given its major contribution to child mortality in Malawi and globally.

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Can cash break the cycle of educational risks for young children in high HIV–affected communities? A cross–sectional study in South Africa and Malawi

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Background Household cash grants are associated with beneficial outcomes; enhanced if provided in combination with care.

Objectives This study describes the impact of cash grants and parenting quality on 854 children aged 5–15 (South African and Malawi) on educational outcomes including enrolment, regular attendance, correct class for age and school progress (controlling for cognitive performance). Consecutive attenders at randomly selected Community based organisations were recruited. The effects of cash plus good parenting, HIV status and gender were examined.

Results Overall 73.1% received a grant – significantly less children with HIV (57.3% vs 75.6% ($\chi^2 = 17.21$, $P < 0.001$). Controlling for cognitive ability, grant receipt was associated with higher odds of being in the correct grade (odds ratio (OR) = 2.00; 95% confidence interval (CI) = 1.36, 2.95), higher odds of attending school regularly (OR = 3.62; 95% CI = 1.77, 7.40), and much higher odds of having missed less than a week of school recently (OR = 8.95; 95% CI = 2.27, 35.23). Grant receipt was not associated with how well children performed in school compared to their classmates or with school enrolment. Linear regression revealed that grant receipt was associated with a significant reduction in educational risk (B = –0.32, $t(420) = 2.84$, $P = 0.005$) for girls.

Conclusion Cash plus good parenting affected some educational outcomes in a stepwise manner, but did not provide additive protection.

Cash transfers are an effective intervention to enhance child outcomes in a number of studies [1,2]. Cash transfer initiatives were first considered in areas of poverty and deprivation, mainly in South America [3,4]. The concept was based on the premise that a regular small cash allowance to families would enhance specific child development outcomes such as immunisation, birth certification, educational and health outcomes [5,6]. This was mediated by the provision of parenting programmes, health programmes and in some instances linking the cash allowance to conditions, such as requiring parents to obtain birth certification and immunisation of the child. The early evaluation literature was concerned with the efficacy of conditional vs unconditional payments. Both were found to be effective, and both had beneficial child developmental outcomes [7]. The challenge with the conditional approach was that the conditions had the benefit of

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prompting uptake of important behaviours, but a sanctioning or punitive approach to the most vulnerable families when parents were unable to meet the conditions seemed counterproductive. This then evolved to the provision of alternative supports (such as cash buddies) for defaulting groups. Other studies showed that if grants were made non–conditional, the majority of recipients used the cash for the benefit of the child anyway. A recent review and meta–analysis of financial incentives found good evidence that they could promote coverage of several important child health interventions [8].

The HIV/AIDS epidemic brought a further set of child health challenges resulting from illness, death, orphaning and poverty. In addition, a number of HIV–related behaviours emerged that needed prompting, such as HIV testing, medication adherence and clinic attendance. In widely–affected environments of parental and child HIV infection, economic and social challenge and daily poverty, this evidence–based intervention was considered worthy of adaptation to African HIV settings [1,9]. Early studies in Africa explored the benefits of conditional vs unconditional provision [10]. Some studies went further to use cash incentives to promote HIV–avoidance behaviours. Subsequent studies in various countries were set up to examine the efficacy of large cash transfer programmes – in whatever form – on child outcome [11]. In South Africa, an unconditional child grant programme was initiated in the late 90s, as part of a range of social security reforms post–apartheid, and has been found to have a positive impact on a range of child outcomes [12]. As a result, cash grants have improved dramatically in terms of availability in the region, with increasing roll–out of old age pensions and child–focused grants [13,14]. Cash transfers were explored as an effective intervention to reduce risk behaviour, to enhance HIV testing, to remain HIV and STI free [15–17]. Most of the trials have concentrated on adolescent behaviour and outcome s[18] or explored the more cash incentive components [8]. Outside of trials, it was important to monitor the impact of cash grants or cash injections on both direct recipients and wider family or household members [19]. This was particularly relevant to children within the recipient households. Studies using large population samples examined adolescent HIV risk behaviour and showed that cash transfers – the receipt of any regular cash allowance into a family – had specific effects on reducing adolescent girls' HIV risk behavior [20,21]. However, this study showed that there was no similar significant effect on boys. A subsequent analysis explored the broader needs and showed that cash plus psychosocial care not only reduced female HIV risk behaviours more than cash alone, but cash plus care had a significant effect on reducing HIV risk behaviour amongst boys. To date the literature clearly shows that cash transfers within studies and within broader government provision is an effective intervention for child outcomes. Furthermore, it is clear that cash alone is not a magic bullet and there are some groups and some outcomes that are not reached [22]; enhancing provision by looking at a more comprehensive cash plus care shows the additive effects and wider impact when cash is part of a more robust approach to supporting children [23].

This focus on adolescence and adolescent risk behaviours within the HIV setting is important, but tells us little about the effects of cash transfers on the younger child. It is important to understand the effects of early commencement of cash support, and whether receipt could break the cycle of predictions leading to HIV risk behaviours in the first place. A particularly well–established pathway to HIV–risk behaviours is educational failure and/or drop out. Two reviews and subsequent studies have shown that educational attendance and achievement are protective against HIV risk behaviours [24–27]. A recent study [28] examined the risk behaviour of age disparate sex and noted that school enrolment was associated with lower adolescent pregnancy rates. Another recent study showed path models between poor educational outcomes and familial HIV/AIDS, poverty, child internalising problems and gender. The four educational measures included enrolment, attendance, grade progression and concentration [29]. A trial in Malawi [30] showed that a cash transfer programme for adolescent girls based on schooling showed a reduction in HIV and Herpes Simplex, and two new randomised trials in South Africa have both shown protective effects of education on adolescent girls' HIV risk [31,32].

It thus seems important to examine the effects of cash transfer programmes on educational outcomes for younger children – prior to the age of HIV associated risk behaviours – and to examine this essential precursor of risk in an attempt to break the risk cycle. This study was therefore set up to explore the effects of cash grants on educational outcomes in younger children, aged 5–15. The study was set up to examine whether cash grants divert poor educational outcomes for children and thus may serve to interrupt the pathways to risk in later adolescence. If such a relationship between cash and educational outcomes exists, a further analysis would be helpful to see if care, defined as good parenting, enhanced or magnified cash effects on education for both girls and boys. In the context of known cognitive delays related to paediatric HIV–infection, uninfected exposed children [33,34] and poverty, it is also essential to examine whether any positive associations of cash and care on educational outcomes are independent of cognitive

ability and delay. On top of that, it would be worthwhile to see whether the effects of cash and/or care on educational outcomes differ by child HIV status.

METHODS

Participants

The data from this study emerged from the longitudinal Child Community Care study which took place in 2013–2014, tracking the development of children infected and affected by HIV/AIDS who attend community–based organisations (CBOs) in South Africa and Malawi. The CBOs in question were selected from a list composed of all CBOs (n = 588) funded by 11 funding partners (World Vision, Comic Relief, Save the Children, Firelight Foundation, Help Age, UNICEF, REPSSI, Bernard van Leer Foundation, STOP AIDS Now, AIDS Alliance and the Diana Memorial Fund). All 588 CBOs were stratified by funder and 28 were randomly selected, prorated for population size, resulting in 28 CBOs in South Africa and four in Malawi. Ethical approval was obtained from the ethics boards of University College London (reference number 1478/002) and Stellenbosch University (reference number N10/04/112).

All CBO's consented to inclusion in the study. All caregivers received full information outlining the study and clarifying the voluntary nature of participation, the consent procedures for themselves and their child, the confidentiality around the study and the ability to withdraw at any time with no consequences. Caregiver consent was provided in writing and with the process provided orally and on written information sheets for them to keep. In addition assent was gained from all children with standardised and age appropriate information explained. Participation was voluntary and was not paid. Children were provided with a fruit snack and a drink together with a participation certificate, while caregivers were provided with a small food/grocery item. Child protection issues were handled with a full referral procedure in place if required or requested to CBO and local health/social services.

Procedure

Consecutive children between the ages of 5–15 years old and their primary caregivers were interviewed by thoroughly trained data collectors using mobile phone technology [35]. The questionnaires were translated and back–translated into Zulu and Xhosa and the participants were interviewed in the language of their choice. Data were collected in 2013–2014. Participation included 854 children and their primary caregiver.

Measures

Child HIV status was determined using caregiver report. Children were classified either as confirmed HIV–positive or as non–HIV–positive, with the latter comprising both children who were confirmed HIV–negative and children who had never been tested. Caregiver HIV status was assessed using self–report. **Educational outcomes** were assessed using questions from the Child Status Index (CSI) tool [36]. Caregivers were asked to report on children's enrolment in school, access and learning outcomes. This comprised six items: 1) school enrolment ("Is your child enrolled in school?" Response categories were *yes* or *no*); 2) school regular attendance ("Does your child go to school?" Response categories were *yes regularly, yes sometimes, yes but rarely*, or *no*); 3) school non–attendance ("How many school days did the child miss in the past two weeks?" Responses were coded as whether the child missed school days for an extended period (>1 week) during the previous weeks); 4) being in the age–appropriate school grade ("Is your child in the correct class for his or her age?" Response categories were *yes* or *no*); 5) school performance ("How do teachers report your child is doing in school?" Response categories were *he or she does better than most children, he or she does as well as other children,* or *he or she struggles at school*), and 6) learning progress ("Is the child quick to learn when introduced to new chores and things?" Response categories were *yes, no* or *don't know*). All six items were converted into a binary (yes/no) variable. **Educational risk** was a composite measure made up of five binary variables. This included incorrect school grade for age, irregular school attendance, rated as a slow learner, reported as struggling in school, and missing more than a week of school recently. For each affirmative answer to these five questions, the child's educational risk score increased by one, resulting in a total score ranging from 0–5 – with the higher score indicating higher educational risk. **Grant receipt** (any/none) was determined based on whether the caregivers reported receiving one or more of the following grants into the home: a retirement pension, state pension, disability grant, child support grant, foster child grant, or care dependency grant. **Number of grants** was the num-

ber of grants received in total by a family (range from 0–6). **General cognitive ability** was measured using the draw–a–person task [37,38]. **Good parenting** was operationalized using a composite measure of 10 items (scored by caregiver and child) related to positive parenting, affection and praise, positive discipline tactics, and lack of abuse or violence. Each item was coded as binary and a total score was calculated by summing up the ten items for a scale with a range of 0–10. Scores equal to or above 8 were then coded as good parenting and scores below 8 were coded as not good parenting [39].

Statistical analysis

The statistical analysis comprised five steps. First, t—tests and chi–square tests were run to look at differences between those receiving grants and those not receiving grants on educational variables. Second, associations between grant receipt and educational variables were tested using logistic regressions for binary variables and linear regression for continuous variables. These were also carried out split by gender. Third, linear and logistic regressions were conducted to test for interaction effects of gender and grant receipt on educational outcomes to explore whether gender was a moderating factor. Fourthly, the same series of linear and logistic regression analyses were carried out, but with an interaction between grant receipt and child HIV status included to observe whether child HIV status was a moderating factor on the associations between grant receipt and educational outcomes. Lastly, a series of regression models were used to examine associations of cash only, good parenting care only, and both cash and good parenting (represented by dummy variables, taking "neither" as the reference category) with educational outcomes. The analyses in the second, third, and fourth steps were all adjusted for general cognitive ability and age. Steps two and four were also adjusted for gender except in cases where gender was looked at as the predictor of interest (ie, in step two the analysis of the total sample is adjusted for gender, but not the analyses that are split by gender). All regression analyses were carried out separately for each educational outcome.

RESULTS

In total, 854 children (52.3% girls; aged 5–15, M = 10.21, SD = 2.80) and their caregivers were interviewed (total participant N = 1708) (**Table 1**). There were 116 children (13.9%) reported as HIV+ve by their caregiver. Of the 808 caregivers, 160 (19.8%) were themselves HIV+ve. Of the 854 children, 46% were cared for by their biological parent/s and 54% by other caregivers (grandparents 28.7%). The caregivers of

Table 1. Cross–sectional differences between those receiving cash transfer and those not receiving cash transfer on educational outcomes, split by child HIV status*

	Cash grant (n = 624)			No cash grant (n = 230)			Difference statistic (P–value)
	Total	HIV–positive children (n = 69)	Non–HIV–positive children (n = 557)	Total	HIV–positive children (n = 46)	Non–HIV–positive children (n = 180)	
Educational risk	**0.71 (1.01)**	1.22 (1.27)	0.65 (0.95)‡	**1.11 (1.23)**	1.26 (0.98)	1.07 (1.28) ‡	4.28 (<0.001)
Enrolled in school	**620 (99.4%)**	69 (100%)	551 (99.3%)†	**222 (96.5%)**	45 (97.8%)	177 (96.2%)†	9.77 (0.002)
Correct class for age	**468 (75.5%)**	38 (55.1%)	430 (78.0%)‡	**107 (48.2%)**	18 (40.0%)	89 (50.3%)‡	56.20 (<0.001)
Regular attendance	**601 (96.9%)**	63 (91.3%)	538 (97.6%)‡	**198 (89.2%)**	40 (88.9%)	158 (89.3%)‡	20.24 (<0.001)
Quick learner	443 (72.6%)	42 (61.8%)	401 (74.0%)	164 (74.5%)	28 (65.1%)	136 (76.8%)	0.30 (0.58)
Doing as well or better than most in school	522 (84.2%)	47 (68.1%)	475 (86.2%)	183 (82.4%)	37 (82.2%)	146 (82.5%)	0.37 (0.54)
Missed less than a week of school	**616 (99.4%)**	69 (100%)	547 (99.3%)‡	**210 (94.6%)**	44 (97.8%)	166 (93.8%)‡	19.87 (<0.001)
Working memory	**9.34 (3.54)**	8.25 (3.78)	9.47 (3.49) ‡	**7.98 (3.44)**	7.16 (3.50)	8.19 (3.41) ‡	4.93 (<0.001)
General cognitive ability	**95.29 (14.92)**	92.74 (15.05)‡	95.60 (14.89) ‡	**80.34 (18.47)**	69.62 (19.16) ‡	83.00 (17.34) ‡	10.93 (<0.001)

*Symbols denote differences on educational outcomes between HIV–positive and HIV–negative children within their grant category (ie, HIV–positive children whose caregivers receive a grant are compared with HIV–positive children whose caregivers do not receive a grant, and non–HIV–positive children whose caregivers receive a grant are compared with non–HIV–positive children whose caregivers do not receive a grant). The difference statistic (P–value) denotes the differences between children receiving a grant and not receiving a grant, regardless of child HIV status. Bolded variables differed significantly in the total sample according to grant receipt. Numbers occasionally do not add up to the total due to missing data.
† $P<0.01$.
‡$P<0.001$.

73.1% of all children reported receiving at least one cash grant, and 26.9% reported receiving no grant whatsoever. Grant receipt did not differ according to child gender (caregivers of 72.3% of the boys and 73.3% of the girls received a grant; $\chi^2_1 = 0.13$, $P = 0.72$). Grant receipt did differ significantly according to child HIV status, with 57.3% of the HIV–positive children receiving a grant compared to 75.6% of the non–HIV–positive children ($\chi^2_1 = 17.21$, $P < 0.001$).

Associations between grant receipt and educational risk

Independent of general cognitive ability, grant receipt was associated with a number of beneficial educational outcomes. As can be seen in **Table 2**, children in households receiving grants within the past year had higher odds of being in the correct grade for their age (OR = 2.00; CI = 1.36, 2.95), higher odds of attending school regularly (odds ratio (OR) = 3.62; 95% confidence interval (CI) = 1.77, 7.40), and much higher odds of having missed less than a week of school recently (OR = 8.95; 95% CI = 2.27, 35.23). However, these children also had significantly lower odds of being quick learners (OR = 0.62; 95% CI = 0.42, 0.93). Grant receipt was not associated with how well children performed in school compared to their classmates or with school enrolment in the total sample. Some of these findings were gender–specific; while the findings on attendance were comparable for boys and girls, only girls had a positive association between grant receipt and being in the correct grade (OR = 2.52; 95% CI = 1.42, 4.44). Furthermore, only for boys grant receipt was associated with lower odds of being a quick learner (OR = 0.48; 95% CI = 0.28, 0.83) and lower odds of doing as well or better than most in school (OR = 0.51; 95% CI = 0.27, 0.96). Finally, a linear regression revealed that grant receipt was not significantly associated with total educational risk for the entire sample (B = –0.14, $t(800) = 1.55$, $P = 0.12$), and also not for boys specifically (B = 0.028, $t(377) = 0.20$, $P = 0.84$). However, for girls, grant receipt was associated with a significant reduction in educational risk (B = –0.32, $t(420) = 2.84$, $P = 0.005$).

Moderation analysis: Gender

Moderation analyses for an interaction effect between child gender and grant receipt on educational outcomes only uncovered an interaction effect on the child being in the correct grade for their age (OR = 1.97; 95% CI = 1.01, 3.84; **Figure 1**). This shows that while for both genders the odds of being in the correct grade for their age improved somewhat as a result of grant receipt, the improvement of girls as a result of cash transfer was significantly larger than the improvement of

Figure 1. Moderation effect of gender on the association between grant receipt and being in the correct grade for age (odds ratio (OR) = 1.97; 95% confidence interval (CI) = 1.01, 3.84; P = 0.048).

Table 2. Cross–sectional logistic regression outcomes of receiving cash transfer (0 = no, 1 = yes), or cash plus care (0 = no cash and no care, 1 = either cash or care, 2 = cash plus care) on educational outcomes*

	Model 1: OR (95% CI)			Model 2: OR (95% CI)		
	Total	**Boys**	**Girls**	**Total**	**Boys**	**Girls**
Enrolled in school	4.27 (0.94, 19.41)	9.48 (0.87, 103.53)	2.07 (0.29, 14.85)	1.72 (0.55, 5.40)	4.00 (0.57, 28.37)	1.01 (0.24, 4.24)
Correct class for age	2.00 (1.36, 2.95)§	1.58 (0.93, 2.68)	2.52 (1.42, 4.44)‡	1.31 (0.98, 1.74)	1.04 (0.70, 1.55)	1.64 (1.08, 2.51)†
Regular attendance	3.62 (1.77, 7.40)§	4.27 (1.53, 11.93)‡	3.18 (1.15, 8.83)†	1.97 (1.10, 3.52)†	2.13 (0.91, 5.03)	1.85 (0.84, 4.11)
Quick learner	0.62 (0.42, 0.93)†	0.48 (0.28, 0.83)‡	0.90 (0.49, 1.65)	0.84 (0.63, 1.10)	0.61 (0.42, 0.90)†	1.21 (0.80, 1.81)
Doing as well or better than most in school	0.70 (0.44, 1.14)	0.51 (0.27, 0.96)†	1.20 (0.56, 2.57)	0.92 (0.66, 1.29)	0.72 (0.46, 1.12)	1.32 (0.77, 2.28)
Missed less than a week of school	8.95 (2.27, 35.23)‡	10.81 (1.17, 100.30)†	8.37 (1.42, 49.26)†	3.95 (1.38, 11.32)†	5.29 (0.96, 29.03)	3.28 (0.84, 12.78)

OR – odds ratio, CI – confidence interval

*Model 1 is effect of receiving a cash transfer adjusted for general cognitive ability, child age and child gender. Model 2 is the effect of receiving cash plus care, either or neither, adjusted for the same covariates. Analyses for all educational outcomes were done separately.

†$P < 0.05$.

‡$P < 0.01$.

§$P < 0.001$.
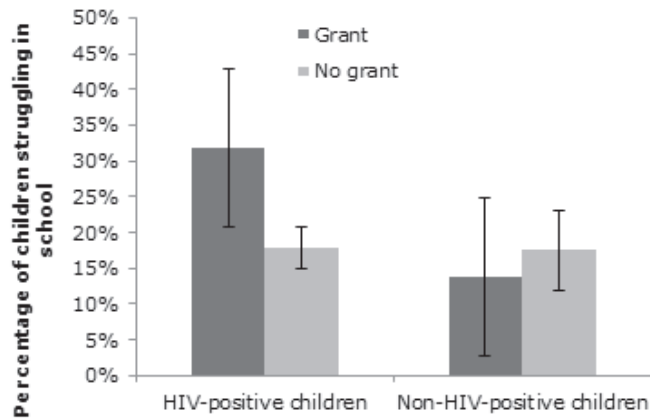
Figure 2. Moderation effect of child HIV status on the association between grant receipt and school performance (odds ratio (OR) = 0.34; 95% confidence interval CI = 0.11, 1.004; P = 0.051).

boys. 50.4% of the girls whose households did not receive a grant were in the correct grade compared to 83.4% of the girls whose households did receive a grant. For the boys, 45.4% of those not receiving grants were in the correct class, compared to 66.3% of those who did receive a grant. On the other educational outcomes, no moderation effect of gender was found.

Moderation analysis: Child HIV status

A marginally significant moderation effect of child HIV status (**Figure 2**) was found on the association between receiving a grant and struggling in school (OR = 0.34; 95% CI = 0.11, 1.004, P = 0.051), on top of the main effects of child HIV (OR = 8.64; 95% CI = 1.91, 39.01, P = 0.005) and grant receipt (OR = 0.10; 95% CI = 0.01, 0.74, P = 0.024). Upon further inspection, this was due to the fact that even though within the non–HIV–positive children those receiving and not receiving a grant have similar proportions of children struggling in school (13.8% and 17.5% respectively), among the HIV–positive children receiving a grant was associated with much more struggling in school (31.9%) than among the children whose caregivers do not receive a grant (17.8%). On other educational outcomes (school attendance, educational risk, being in the correct class for age, being a quick learner, and having missed school for more than a week recently), no moderation effect of child HIV was found. A moderation analysis on school enrolment could not be performed because all HIV–positive children were enrolled in school.

Associations between grant receipt (cash) and good parenting (care) on educational outcomes

Of the total, 21.0% of the children (n = 179) did not receive cash or good care, 61.4% of the children (n = 524) received either cash or good care, and 17.7% of the children (n = 151) received both cash and care. In a linear regression model, receiving cash, care or a combination of both was not associated with educational risk for the total sample (B = −0.068, t(800) = 1.10, P = 0.27), or for boys (B = 0.086, t(377) = 0.85, P = 0.39). For girls, however, receiving cash, care, or a combination of both was associated with a reduction in educational risk in a stepwise manner (B = −0.20, t(420) = 2.66, P = 0.008).

As can be seen in **Table 2**, cash or care and cash plus care was not associated with most of the other education outcomes. However, it was associated in a stepwise manner with higher odds of regular attendance in the total sample (OR = 1.97; 95% CI = 1.10, 3.52) and higher odds of having missed less than a week of school (OR = 3.95; 95% CI = 1.38, 11.32). For girls (OR = 1.64; 95% CI = 1.08, 2.51) but not for boys (OR = 1.04; 95% CI = 0.70, 1.55) cash and/or care was associated with higher odds of being in the correct grade for age. For boys (OR = 0.61; 95% CI = 0.42, 0.90) but not girls (OR = 1.21; 95% CI = 0.80, 1.81) it was associated with lower odds of being a quick learner.

Upon further inspection, only the step from receiving no cash and no care to receiving either cash or care was associated with a significant improvement in educational outcomes (**Table 3**).

For both boys and girls receiving cash or care was associated with a higher likelihood of being in the correct class for their age ($\chi^2_1 = 7.41$, P < 0.01 and $\chi^2_1 = 28.91$, P < 0.001, respectively) and a higher likelihood of regular attendance ($\chi^2_1 = 9.67$, P < 0.01 and $\chi^2_1 = 8.57$, P < 0.01, respectively). On top of that, for girls but not for boys receiving cash or care was also associated with lower educational risk (mean (M) = 0.55, standard deviation (SD) = 0.93) compared to not receiving either (M = 1.03, SD = 1.10; t(342) = 4.02, P < 0.001; **Figure 3**). Receiving cash plus
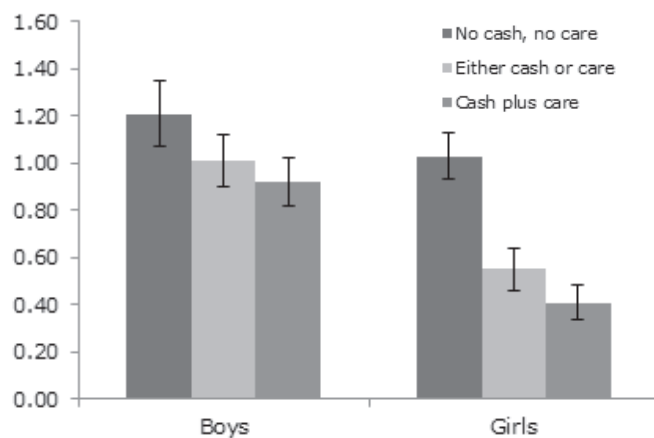
Figure 3. While for boys receiving either cash or care was not associated with significantly lower educational risk than receiving no cash and no care (t(328) = 1.29, P = 0.20), this difference was significant for girls (t(342) = 4.02, P < 0.001). For neither gender receiving cash plus care was better than receiving either cash or care.

Table 3. Cross–sectional one–way ANOVA and chi–square results of receiving no cash or care, either cash or care, or cash plus care on cognitive abilities and educational risk*

	Boys (n = 400)						Girls (n = 439)					
	No cash, no care (A)	Cash or care (B)	Cash plus care (C)	Difference statistic (P–value)	Post–hoc A vs B (95% CI)	Post–hoc B vs C (95% CI)	No cash, no care (A)	Cash or care (B)	Cash plus care (C)	Difference statistic (P–value)	Post–hoc A vs B (95% CI)	Post–hoc B vs C (95% CI)
Educational risk	1.21 (1.38)	1.01 (1.15)	0.92 (1.06)	1.22 (0.30)	0.20 (–0.16, 0.56)	0.09 (–0.32, 0.50)	1.03 (1.10)	0.55 (0.93)	0.41 (0.70)	11.59 (<0.001)	0.49 (0.21, 0.76)‡	0.14 (–0.14, 0.42)
Correct class for age	39 (47.0%)	161 (63.9%)	40 (65.6%)	5.23 (0.016)	7.41‡	0.061	44 (50.0%)	208 (79.7%)	71 (85.5%)	37.08 (<0.001)	28.91‡	1.41
Regular attendance	73 (88.0%)	244 (96.8%)	59 (96.7%)	10.72 (0.005)	9.67†	0.002	79 (89.8%)	254 (97.3%)	79 (95.2%)	8.49 (0.014)	8.57†	0.93
Quick learner	58 (70.7%)	159 (64.1%)	38 (63.3%)	1.33 (0.52)	1.20	0.013	67 (77.0%)	202 (78.6%)	71 (85.5%)	2.32 (0.32)	0.10	1.91
Doing well or better than most in school	65 (78.3%)	190 (75.4%)	51 (83.6%)	1.95 (0.38)	0.29	1.87	76 (86.4%)	234 (89.7%)	78 (94.0%)	2.72 (0.26)	0.72	1.39

CI – confidence interval

*Difference statistic is F for continuous variables and χ2 for categorical variables. Post–hoc comparisons are mean difference (odds ratio) between categories for continuous variables (ie, A–B and B–C) and χ2 for categorical variables. Because half of the cells in school enrolment and school days missed had fewer than five cases, a chi–square analysis for these variables split by gender could not be carried out.

†$P<0.01$.

‡$P<0.001$.

care as opposed to only cash or only care, however, was not associated with statistically better educational outcomes for either of the two genders.

DISCUSSION

This analysis has several implications for understanding the role of both cash grants and care provision for young children. First, our data show that receiving a grant was associated with beneficial educational outcomes: higher odds of being in the correct class for age, higher odds of regular school attendance, and higher odds of having missed less than a week of school recently. This is despite the fact that primary education in both countries studied is provided free of charge and enrolment for the overall sample was high. Previous South African research on the impact of the child support grant in particular on educational outcomes has found a positive impact on enrolment. Samson et al. [40] found increased school attendance among beneficiaries, while a study looking specifically at adolescent recipients were more significantly more likely to be enrolled than those not receiving the grant, after controlling for a range of factors [41]. However, our data show that the impact may extend further than enrolment only, which is important given that children may be enrolled but not allowed to attend because they have not been able to pay even small required fees or extra costs associated with attendance. We also found that receiving a grant was also associated with lower odds of being a quick learner. This may be a cause of grant receipt rather than a consequence; it might be that children who display symptoms of cognitive delay or disability are more likely to receive a grant in the first place and indeed may have higher needs.

Second, our data show different levels of access based on child characteristics. The HIV–positive children were less likely to receive a grant, and those who received a grant were more likely to struggle in school, perhaps also reflecting that the most needy (ie, the ones who struggle in school) more often receive a grant or come to the attention of those referring or processing grants. It may be that particular grants linked to disability are within the eligibility for some children with HIV. Indeed this is in line with findings from a study in Zimbabwe which showed that orphaned children were at a higher risk of poor social protection outcomes [19]. This finding highlights the particular needs of families affected by HIV who should be more likely to receive grants – but were less likely in our study. It may be that illness or a distraction of focus actually overlooks this need. A clear learning imperative is for clinics to check and streamline grant access for HIV positive children.

Our data also point to some consistent variation by gender, which suggests the importance of disaggregating the data by gender and perhaps considering provision with a gender focus. There were some differences between boys and girls in our findings. While the educational outcomes for both genders was associated with a significant improvement for those in receipt of a cash grant, girls improved more than boys on the variable related to correct grade for age. Also while receiving either cash or good parenting

was associated with significantly lower overall educational risk for girls, this was not the case for boys. Similar variations in educational achievement outcomes associated with grant receipt have been noted in previous research on the South African grant system, with the child support grant associated with better attendance for boys in particular, and higher grade attainment, for girls [12].

Unlike the literature on HIV risk behaviour for older adolescence, our younger sample showed that receiving cash plus care did not improve educational outcomes over and above receiving either cash or care. This was the case for both girls and boys with comparable results for both genders. It may be that either is associated with educational outcomes or that with younger children the additive effect is not yet obvious. No measure on the quality of the educational experience was gathered in this study and the next step in provision may be to ensure high quality education for those who do attend and not simply count enrolment and attendance as sufficient. Perhaps the care components in this study, which were measured as good parenting, are important in their own right for educational outcomes. Other care variables utilised in adolescent studies are not necessarily relevant or available to younger children who may not, for example be able to attend support groups independently.

The study is not without limitations. This study is carried out within a community setting, in organisations that serve the most vulnerable children [42]. The respondents were gathered from CBO attenders and thus it is difficult to say if the sample is representative of the larger community. It is also possible that these organisations were facilitating both cash grant access and care provision. This needs to be taken into consideration when generalising the findings to the wider community. Despite this, grant access was not universal with approximately three quarters of caregivers receiving a grant. As the data was cross–sectional there is no way of determining causal pathways but can only demonstrate associations for further investigation. Longitudinal data would be essential to track early educational benefits into adolescence with the possibility of assessing impacts on HIV risk behaviour in the first place and ultimately sexually transmitted infections and HIV incidence. HIV status was established using caregiver report and was not confirmed using biological tests. Such reporting has been used in many studies, but without confirmatory tests it is possible that the HIV status was underestimated from those who did not wish to disclose. Educational measures would have been strengthened with teacher or school reports. In addition, it would be of value for future research to examine impacts of social protection on educational achievement for children of different ages (from early childhood development to tertiary education) and in different schooling environments. Good parenting was the only domain used to determine care. Using a more comprehensive model of care (care in the home, care at school, and care in the community) or broader parenting competencies such as skill building, might lead to different results, but no such broader care variables were gathered.

Yet, despite these limitations, these data clearly show the advantages of cash grants for a number of educational outcomes. Educational risk is a pathway for future behavioural risk, and it appears that grants may be associated with improved educational outcomes and may well interrupt the causal cycle seen in later adolescence. In other areas of child development there is clear evidence that early intervention is beneficial and that prevention of a problem is better than having to undo a problem once it is entrenched. This data thus lends support for the importance of both cash grants and good parenting defined as care on educational pathways for young children, as an investment in its own right, but also as an investment for their future. For HIV positive children, access to grants may be specifically beneficial, yet they are less likely to receive these. Integrated clinic provision may well enhance child development by including referral for grants within the package of services offered. Special attention to school and educational factors is needed for HIV positive children who may struggle academically. Many of the early conditional cash transfer studies used school enrolment as a condition. Our data suggests that in countries with universal provision of primary school, attention needs to focus on more detailed educational variables including attendance, progress and achievement. Cash grants as well as care appear to be associated with benefits on these educational outcomes for vulnerable children.

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The cost of diabetes in Latin America and the Caribbean in 2015: Evidence for decision and policy makers

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Background The financial implications of the increase in the prevalence of diabetes in middle–income countries represents one of the main challenges to health system financing and to the society as a whole. The objective of this study was to estimate the economic cost of diabetes in Latin America and the Caribbean (LAC) in 2015.

Methods The study used a prevalence–based approach to estimate the direct and indirect costs related to diabetes in 29 LAC countries in 2015. Direct costs included health care expenditures such as medications (insulin and oral hypoglycemic agents), tests, consultations, hospitalizations, emergency visits and treating complications. Two different scenarios (S1 and S2) were used to analyze direct cost. S1 assumed conservative estimates while S2 assumed broader coverage of medication and services. Indirect costs included lost resources due to premature mortality, temporary and permanent disabilities.

Results In 2015 over 41 million adults (20 years of age and more) were estimated to have Diabetes Mellitus in LAC. The total indirect cost attributed to Diabetes was US$57.1 billion, of which US$ 27.5 billion was due to premature mortality, US$16.2 billion to permanent disability, and US$ 13.3 billion to temporary disability. The total direct cost was estimated between US$ 45 and US$ 66 billion, of which the highest estimated cost was due to treatment of complications (US$ 1 616 to US$ 26 billion). Other estimates indicated the cost of insulin between US$ 6 and US$ 11 billion; oral medication US$ 4 to US$ 6 billion; consultations between US$ 5 and US$ 6 billion; hospitalization US$ 10 billion; emergency visits US$ 1 billion; test and laboratory exams between US$ 1 and US$ 3 million. The total cost of diabetes in 2015 in LAC was estimated to be between US$ 102 and US$ 123 billion. On average, the annual cost of treating one case of diabetes mellitus (DM) in LAC was estimated between US$ 1088 and US$ 1818. Per capita National Health Expenditures averaged US$ 1061 in LAC.

Conclusions Diabetes represented a major economic burden to the countries of Latin America and the Caribbean in 2015. The estimates presented here are key information for decision–making that can be used in the formulation of policies and programs to achieve greater efficiency and effectiveness in the use of resources for diabetes prevention in the 29 countries of LAC.

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The cost of diabetes mellitus (DM) was estimated at US$ 65 billion in 2000 in Latin America and the Caribbean (LAC) [1]. This burden was attributed to lost productivity due to mortality and disability, as well as direct medical costs caused by treating diabetes and its long–term complications.

The financial implications of the increase in the prevalence of diabetes in middle–income countries, represents one of the main challenges to be solved by health systems and society as a whole. DM is one of the top global public health concerns because of the increased morbidity and mortality among affected individuals. An estimated 415 million people suffer from diabetes globally in 2015 and this number is expected to reach the 642 million mark by 2040 [2]. This will increase direct health expenses as well as premature deaths and disability to unprecedented levels unless effective preventive and control strategies are implemented.

DM presents a global public health challenge, particularly among middle and low–income countries, where 80% of those with the disease live. Diabetes management is complex because it demands continuous care involving many services, tests, and medications, owing to the detrimental effect of chronic hyperglycemia on organs and tissues.

According to the 2012 World Health Organization (WHO) National Capacity Survey for Non Communicable Diseases (NCD) Prevention and Control, 95% of countries in the Americas reported having DM policies or action plans. However, the capacity to prevent and control diabetes may be limited. In fact, only one third of the countries reported having operational evidence–based guidelines or protocols [3]. Population–based surveys and clinical series from many of the countries of LAC indicated that most people with diagnosed DM do not achieve treatment goals [4–9], increasing the risk of premature mortality and disabilities.

The objective of this study was to estimate the economic cost of diabetes in LAC in 2015. This study intends to update a previous estimate of the cost of diabetes in LAC for 2000 [1].

METHODS

This study used a prevalence–based approach that includes direct and indirect costs caused by diabetes. Adult (20 and more years of age) diabetes prevalence data for 2015 were used to estimate the direct and indirect costs related to diabetes in 29 LAC countries (Latin America: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Uruguay and Venezuela; English Caribbean: Bahamas, Barbados, Belize, Grenada, Guyana, Jamaica, Saint Lucia, Suriname and Trinidad & Tobago). Estimates included people with both type 1 and type 2 diabetes. The protocol for this project was reviewed and approved by the Committee on Health Research of the National Council of Science and Technology of Mexico. Patient records information was anonymized and de–identified prior to analysis.

Data

Direct costs included insulin and oral hypoglycemic agents, consultations, A1c tests, lipid profiles, micro albuminuria test, hospitalizations, emergency visits and treating complications. A "bottom–up" approach was used for direct cost estimation.

Indirect costs included lost resources due to mortality, as well as temporary and permanent disabilities. These were estimated using the human capital approach, which applies the present value of future earnings to estimate the burden of mortality and disability [10].

LAC demographic data for 2015 [11] were combined with prevalence data for 2015 from the International Diabetes Federation (IDF) to estimate the population with diabetes by age and gender for each country. Countries were classified using the World Bank GDP per capita classification [12] in low–income countries (US$ 1035 or less), lower middle–income countries (US$ 1036 to US$ 4085), upper middle–income countries (US$ 4086 to US$ 12 615), and high–income countries (US$ 12 616 or more) [13]. The most recent National Health Expenditures (NHE) for each country were obtained from the Pan American Health Organization (PAHO) basic data indicators [14]. NHE for Puerto Rico was not available.

Five sources of original country data were used to produce estimates:

1. Commercial prices reported to the NCD Management National Capacity survey for chronic diseases in LAC [15] were obtained for tests, medications, and medical services. Prices were updated in 2015 by

contacting health professionals and diabetes associations in each country. The PAHO database contains prices for insulin, oral medication, testing and services for 26 out of the 29 countries [15]. When a specific price for one country was not available we used an average price for countries of the same sub region (English Caribbean, Central or South America). The price list is available in **Online Supplementary Document**.

2. The Sentinel Surveillance (ViCen) questionnaire was completed for a random sample of 1899 patients in clinics in six countries (Bolivia, Chile, El Salvador, Guatemala, Honduras and Nicaragua). This survey explored health care utilization along with the presence of DM and diabetes–related long–term complications. The ViCen questionnaire was produced by PAHO in collaboration with the IDF and was used in previous research in Brazil [16,17].

3. A clinical record database of 51 795 patients from Chile was used to calculate the prevalence of chronic complications (retinopathy, nephropathy, cardiovascular disease, neuropathy and peripheral vascular disease) [18]. This database was also used to produce estimates of permanent disability by age and sex adjusted by diabetes duration.

4. A database from the National Institute of Public Health (NIPH) in Mexico was used to estimate the cost of cases with and without long–term diabetes complications. The NIPH database provided an estimation of how much higher was the cost of cases with each long–term diabetes complication as compared to treating cases without complications [19].

5. The Barbados Eye Study (BES) is a cohort study funded by the National Eye Institute. It is a nationally representative cohort of 4709 Barbados–born citizens, ages 40 to 84 years and selected by simple random sampling. BES used Relative Risk Ratios (RR), based on the hazard ratios estimated from the Cox Proportional Hazard Model. RR was calculated comparing mortality for people with and without diabetes by age and gender using 9–year follow–up data (1997–2002) [20].

Direct costs

Two analyses were conducted separately to calculate direct cost. These analyses are identified as Scenario 1 (S1) and Scenario 2 (S2). S1 and S2 differ in estimations for the use of medication and the cost increase related to treatment of diabetes chronic complications. S1 contains conservative estimates while S2 assumes broader coverage of medication and services. Assumptions for S1 and S2 are described below. A sensitivity analysis was conducted to compare results of the cost for S1 and S2.

Medication

Insulin. The annual total cost of insulin (TCI) for the 29 LAC countries was estimated as follows:

$$TCI = NIU \times CI \times IC \quad (1)$$

where NIU is the number of insulin users, CI is the cost of insulin per unit in each country, and IC is the number of insulin unit consumption per year.

Patterns of insulin use might be different in each country. Population based research indicated that among people with diabetes insulin use ranged from 2% in Chile [4] and 29% in Costa RicaRica [7]. Due to the paucity of information regarding the heterogeneity in the use of insulin use, we estimated two different proportion of insulin use: 10% (S1) and 20% (S2) of the diabetes population of each country.

Insulin consumption was assumed at 10 000 IU per person per year, as previously used by Phillips and Salmeron [21] and used in our previous analysis also [1]. The commercial cost of insulin in each country was taken from the PAHO database price list [15].

Oral hypoglycemic agents. The annual total cost of oral medications (TCO) for the 29 countries studied was estimated as follows.

$$TCO = NOU \times CO \times OC \quad (2)$$

where NOU is the number of oral medication users, CO is the cost of oral medications (metformin) in each country extracted from the PAHO database, and OC is the estimated number of pills consumed per person each year.

The proportion of people taking oral medication varies from 90% in Cuba [22] to 50% in Belize [7]. As the proportion of people with diabetes taking oral medication might vary among countries two different

assumptions were applied. We assumed that 50% or 80% of people with diabetes were taking oral medication for S1 and S2, respectively. The per capita consumption of metformin each year was estimated at 1 500 tablets. Prices of Metformin 800 mg were taken from the PAHO database [15].

Consultations and hospitalizations

The total number of consultations and hospitalizations in the general population of each country was obtained from the PAHO basic indicator database [14]. These consultations and hospitalizations were considered to be due to general causes not related to diabetes.

The ViCen survey showed that people with diabetes made 3.5 times more medical visits and had 7 times more hospitalizations than people without diabetes [16]. In addition, the ViCen study showed that length of stay for those with diabetes was 1.9 days longer than those without diabetes [16]. The numbers of medical visits and hospitalization per inhabitants in each country were multiplied by factors of 2.55 and 6, respectively, which represented the excess number of visits and hospitalizations due to diabetes [6,7]. The estimated number of people with diabetes was then multiplied by these products. In the case of hospitalizations, we obtained the total number of hospital days by multiplying the number by the average of length of stay in each country reported to the PAHO basic indicator database [14], and then increased by the fraction of 0.9 which was the excess number of days attributed to diabetes reported by patients to the ViCen study [16]. The costs of consultations and per–day hospitalization were obtained from PAHO's price list [15]. The cost of services, procedures or treatment was not included due to the paucity in country–specific data.

The annual total cost of consultations (TCC) was estimated as follows:

$$TCC = [(NC \times CC) \times COC] \times DM \ (4)$$

where NC is the number of consultations per year, CC is the average cost of a general medicine consultation in each country, COC is the average cost of a consultation with an ophthalmologist in each country, and DM is the number of people under care. It was assumed that, across the region, 55% of those with DM were treated by a health care providers.

The annual total cost of hospitalizations (TCH) was estimated as follows:

$$TCH = NH \times LH \times CH \times DM \ (5)$$

where NH is the annual number of hospitalizations, LH is the length of stay, CH is the average cost of a hospitalization, and DM is the number of those with diabetes who were at risk of being hospitalized. It was assumed that the total number of those with DM was at risk of being hospitalized.

The costs of hospitalizations related to DM and for general causes were calculated separately. Only the excess cost attributed to DM was included in the direct cost calculation. The cost of one day hospital stay was taken from the PAHO's price list [15]. This cost does not include any service or procedure. This cost is assumed to be conservative since it is well known that most cases of diabetes would require specific services and specialized care which are usually more expensive.

The average cost of a general and ophthalmologist medical visit per country was taken from the PAHO database [15].

The cost of medical visits related to DM and for general causes were calculated separately; only the excess cost estimated for those consultations attributed to DM was included in the direct cost calculation. The cost of consultation to a general practitioner in each country was taken from PAHO's price list [15] and was used as a proxy for all DM medical consultations because country specific prices for specialist visits (except for ophthalmologist) were not available. This cost does not include any additional procedures, it includes only a consultation with a physician.

Testing

The annual total cost of examinations (TCE) for the 29 countries was estimated as follows:

$$TCE = (A1c \times Lipid + EKG + Rx + Protein) \times DM \ (3)$$

where A1c is the cost of a glycated hemoglobin test, Lipid is the cost of a lipid profile, EKG is the cost of an electrocardiogram, Rx is the cost of a chest x–ray, protein is the cost of a urine protein test, and DM is the total population with diabetes.

It was assumed that each person with DM was tested once a year with lipid profile, one electrocardiogram, one chest x–ray, and one urine protein test. The number of A1c test was assumed to be 1 per year for S1 and 3 per year for S2.

Emergency visits

The annual total cost of emergency visits (TCEV) was estimated as follows:

$$TCEV = NEC \times CEV \times DM \quad (6)$$

where NEC is the average annual number of emergency visits, CEV is the average cost of an emergency visit in each country taken from the PAHO price list, and DM is the total number of people with diabetes in each country.

The ViCent survey showed that those with diabetes made 1.4 emergency visit per year while those without diabetes reported 0.9 visits per year [16]. The estimated number of people with diabetes was multiplied by 1.4 to estimate the number of emergency visit. The cost of an emergency department visit in each country was obtained from the PAHO's price list [15].

The emergency cost does not include the cost of any procedure, it includes only the cost of being seen by a physician in an emergency department. The cost of emergency visits due to general causes was discounted. Only emergency visits attributed to diabetes (0.5 per person per year) were included.

Complications

This study included the cost of the following complications: cardiovascular disease, nephropathy, neuropathy, peripheral vascular disease and retinopathy. It also included the costs of dialysis, hemodialysis, photocoagulation and treating foot–related problems.

Three steps were used to estimate the cost of complications. First, the weighted probability of major complications from the Chilean QUALIDIAB [18] database were applied to the diabetes population to obtain the number of persons with each complication per country. Second, we estimated the cost of regular care for uncomplicated cases of DM for each country. We made different assumptions for regular care for S1 and S2. Population based surveys showed wide variation in the proportion of cases of diabetes under care in different countries. Therefore, we made different assumptions for the two scenarios. For S1 regular care for uncomplicated cases one visit to an ophthalmologist, one A1c, one lipid profile, one urine protein test, one electrocardiogram and one chest x–ray for 55% of the population with diabetes. This was a conservative estimate that was based on protocols available in some of the participating countries. For S2 regular care for uncomplicated cases included one visit to an ophthalmologist, three A1c, one lipid profile, one urine protein test, one electrocardiogram and one chest x–ray for 85% of the population with diabetes.

Available data from Chile [1], Brazil [17], and Mexico [19] showed that the ratio of expenditure per person with diabetes and chronic complications to persons with diabetes without complications was variable. Because of the heterogeneity of health care provision and medical costs across countries, for each complication a lower (S1) and higher (S2) ratio was used to produce two separate estimates. Among the three sources, we selected the lowest estimated cost ratio (S1) and an average of the other two estimates (S2). The ratio used for these calculations were retinopathy 1.09 and 1.86; neuropathy 1.08 and 1.58; Peripheral Vascular Disease 1.06 and 1.81; Cardiovascular Disease 1.23 and 1.86; and Nephropathy 1.76 and 2.96 for S1 and S2 respectively.

Third, we applied the excess of cost of treating (consultations, medications and other procedures) for each complication as per S1 and S2 cost ratio using the cost estimates for uncomplicated cases in each country as per previous calculation.

The total cost of consultations for retinopathy (TCCR) was estimated as follows:

$$TCCR = [(NCR \times CC) + COC] \times DM \times PVR \quad (7)$$

where TCCR is the annual cost of consultations for those with diabetes retinopathy, NCR is the number of consultations per person with DM–related retinopathy, and PVR is the prevalence of retinopathy.

The total cost of consultations for other (TCCO) DM–related complications was estimated as follows:

$$TCCO = \sum_{i \in I} [(NCC_i \times CC) + COC] \times DM \times PV_i \quad (8)$$

where TCCO is the annual cost of consultations for those with DM and long–term complications other than retinopathy, NCC is the number of consultations per person with a DM–related complication other

than retinopathy, PV is the prevalence of the complication, and *i* represents the four complications studied, excluding retinopathy.

The total cost of consultations for complications (TCCC) of those with DM–related complications was estimated as follows:

$$TCCC = TCCR + TCCO \quad (9).$$

The total cost of hospitalizations related to complication (TCHC) was estimated as follows:

$$TCHC = \sum_{i \in I} NHC_i \times LHC_i \times CH \times DM \times PV_i \quad (10)$$

where TCHC is the annual cost of hospitalizations for those with DM–related complications, NHC is the number of hospitalizations by person with DM–related complications, LHC is the length of a patient's hospital stay, CH is the average cost of a hospitalization per person, PV is the prevalence of complications, and i is the set of complications studied.

The used age–weighted probability for each long–term complication was 1.09 for retinopathy, 1.23 for CVD, 2.35 for nephropathy, 1.08 for neuropathy, and 3.35 for PVD [18].

Indirect costs

Mortality costs

Mortality costs were estimated by multiplying the number of DM–related deaths by age range and gender by the number of years of productive life lost (YPLL) for each age by the country GDP per capita. A three percent discount was applied.

The number of DM–related deaths was calculated by multiplying the number of deaths for all causes, by the population attributable–fraction (PAF), which was estimated as follows:

$$PAF = P(RR–1)/1 + [P(RR–1)] \quad (11)$$

where P is the prevalence of DM and RR is the relative risk of death from the disease.

The Barbados Eye Study (BES) is a cohort study that includes RR obtained from the Barbados Eye Study, which contained information from a cohort of people with diabetes. The RR used were Men 40–49 = 3.4 (1.2–9.3); 50–59 = 2.0 (1.0–3.7); 60–64 = 3.2 (2.2–4.7) and Women 40–49 = 2.8 (1.2–6.4); 50–59 = 4.4 (2.4–8.3); 60–64 = 2.3 (1.1–1.9) (19). YPLL were included for individuals dying between the ages of 40 and 64 years. Only deaths estimated to occur between the ages of 40 and 79 years of age were included. YPLL between the ages of 40 and 64 years of ages were calculated since the age of retiring was assumed to be 65 years of age. 95%–Confidence intervals were calculated by applying lower and higher estimates for the OR of original BES data [19].

Disability costs

Permanent disability. The total proportion of people with disability was estimated at 4.2% of the total target population. After discounting cases considered to be related to general causes, we estimated that 3.2% of the target population was disable due to diabetes. Estimates for other diseases and diabetes related disability by age and gender were obtained by applying research results from Gomez de Moura et al [23] to Brazil's national statistics [24]. The probability of diabetes related disability by age and gender was applied to the Chilean database and adjusted throughout a logistic regression by diabetes duration and the presence of chronic diabetes complications that would prevent people to remain in the workforce. These complications were blindness, amputations, strokes and infarction. The age–and–gender specific estimates were multiplied by the number of people with diabetes by age and gender to obtain the number of disabled due to diabetes. We used these estimates to calculate the number of discounted years of productive life lost (YPLL) before the age of 65 years. Only one year of income lost per person was included. GNP per capita for each country was used as a proxy for lost productivity in 2015. The cost of permanent disability was estimated by multiplying the per capita GNP by the number of YPLL.

Temporary disability. Only absenteeism was included as cost of temporary disability. The lack of information on other aspects of temporary disability such as bed days due to illness or care takers and others were not included. Temporary disability costs were calculated by multiplying the number of economically active people with DM by age and gender between the ages of 20 and 64 years, by the number of days lost due to disability by national annual GDP per capita (divided by 365) as a proxy of potential in-

come per day. The number of people that were economically active in each country was calculated by discounting the unemployed as per data published by the World Bank [12]. The number of lost productive days was calculated with data from the ViCen survey [16]. The estimated number of lost days for general causes not related to DM was subtracted from the total lost days. Thus, the number of lost days included were only the excess number attributed to DM.

All costs estimates are presented in 2015 US dollars (US$).

95%–CI for permanent/ temporary disability as well for indirect cost, were calculated by using bootstrap analysis with 1000 replications of age–and–gender specific estimates.

All analysis were performed using SPSS 24 (IBM Analytics, Armonk, New York, USA) and Stata 12 (StataCorp, College Station, Texas, USA).

RESULTS

Over 41 million people were estimated to have DM throughout LAC in 2015. From the total in LAC of those with DM, approximately 97% lived in Latin America (Central–South America, Mexico and the Spanish Caribbean) and 2% in the English Caribbean. Overall, among components of indirect cost, US$ 27.5 billion was attributed to diabetes related premature mortality, US$ 16.2 billion to permanent disability, and US$ 13.3 billion to temporary disability. The total indirect cost was US$ 57.2 (US$ 54.9–60.4) billion (**Table 1**).

Table 2 presents estimates of the cost of medication as well as exams and consultations for scenario 1 (S1) and scenario 2 (S2). Overall 4 to 6 million people with diabetes were estimated to use insulin with an estimated cost between US$ 6.9 to US$ 11.6 billion. The number of oral medication users was estimated between 19.7 and 33.5 million with an estimated cost of US$ 11 to US$ 18 million. The total cost of medication was estimated to be between US$ 11 to US$ 18 million. This shows how sensitive is direct cost to coverage, in particular the number of insulin or oral medication users.

The total number of hospitalization (**Table 3**) was 36 746 from which more than 18 thousand were estimated to be attributed to diabetes causing a burden of more than US$ 10 billion. The estimated number of emergency visit was more than 95 thousand with an estimated cost of more than US$ 1 billion.

Table 1. Data on those with diabetes mellitus (DM) and estimated indirect costs in Latin America and the Caribbean, 2015

Item	Latin America	English Caribbean	Total
Populations 20–79 (×10³)	315 188	2598	317 786
Total No. of people with diabetes (×10³)	41 022	554	41 576
Mortality:			
No. of deaths	1 364 376	22 137	1 386 513
Deaths related to diabetes (40–64 years)	313 205	4897	318 102
YPLL	2 044 418	30 214	2 074 633
Cost (US$×10⁶)	27 280	305	27 585
95% CI (US$×10⁶)	8 066–47 905	90–570	8157–48 475
Permanent disability:			
Total No. of people with permanent disability	1 389 057	17 407	1 406 464
YPLL due to DM	1 016 571	26 557	1 043 128
Cost in 1 year (US$×10⁶)	15 863	342	16 205
95% CI (US$×10⁶)	15 115–16 702	316–517	15 450–17 037
Temporary disability:			
Estimated DM employed population (20–64)	31 463 016	409 686	31 872 702
No. of days missed of work general causes	665 563 904	8 306 850	673 870 754
No. of days missed of work due to DM	309 631 903	3 864 491	313 496 394
YPLL	847 567	10 588	858 154
Cost (US$×10⁶)	13 212	179	13 391
95% CI (US$×10⁶)	12 773–13 735	170–191	12 944–13 906
Indirect cost (US$×10⁶)	56 355	826	57 181
95% CI (US$×10⁶)	54 045–59 565	799–992	54 881–60 411

YPLL – years of productive life lost; CI – confidence interval

Table 2. Direct cost of diabetes mellitus (DM) by in Latin America and the Caribbean (LAC) sub–region, 2015

Item	Latin America		English Caribbean		Total	
	S1	S2	S1	S2	S1	S2
Medication:						
No. of insulin users (×10³)	3869	6550	184	364	4054	6915
No. of oral medication users (×10³)	18851	32046	898	1527	19749	33573
Cost of insulin (US$×10⁶)	6671	10971	324	640	6995	11611
Cost of oral medication (US$×10⁶)	3811	6479	218	370	4029	6849
Total cost of medication (US$×10⁶)	10482	17450	542	1010	11024	18460
Cost of exams (US$×10⁶)	1252	2584	128	274	1380	2859
Consultations:						
Total no. consultations (×10³)	266169	321546	13538	15605	279708	337151
DM related causes (×10³)	101523	156899	3789	5856	105312	162755
Cost DM related causes (US$×10⁶)	4872	6536	196	270	5068	6806

Table 3. Cost of hospitalizations and emergency visit among those with diabetes in Latin America and the Caribbean in 2015

Item	Latin America	English Caribbean	Total
Total No. of hospitalization (×10³)	34747	1998	36746
Diabetes–related causes (×10³)	17462	832	18294
Total days	135834	7843	143677
No. days (DM related causes)	66691	3177	69868
Cost DM related (US$×10⁶)	10025	309	10334
No. emergency visits	91277	4349	95626
Cost (US$×10⁶)	1036	22	1059

DM – diabetes mellitus

Table 4. Estimated number (×10³) of people with diabetes and chronic complications in Latin America and the Caribbean, 2015

Complications	Latin America	English Caribbean	Total
No. person with retinopathy	4671	223	4894
No. person with cardiovascular disease	4496	214	4711
No. person with nephropathy	2306	110	2416
No. person with neuropathy	3421	163	3584
No. person with peripheral vascular disease	2254	107	2362

More than 4 million people with diabetes were estimated to have retinopathy and cardiovascular diseases respectively, while more than 3 million were estimated to have neuropathy and more than 2 million were estimated to suffer from nephropathy or peripheral vascular disease, respectively (**Table 4**).

Treating chronic complications caused an estimated burden between US$ 16.2 and US$ 26.5 billion for S1 and S2 respectively. Cardiovascular disease was the costliest complication with an estimated burden between US$ 5.6 and US$ 8.2 billion followed by retinopathy (US$ 3.5 to US$ 6.4 billion), nephropathy (US$ 2.9 to US$ 4.6 billion), neuropathy (US$ 2.1 to US$ 3.7 billion) and peripheral vascular disease (US$ 2 to US$ 3.4 billion) (**Table 5**).

Among countries of LAC (**Table 6**) the highest direct cost was estimated for Brazil (between US$ 17.5–US$ 23.8 billion); while the lowest was estimated for Grenada (between US$ 4.0–US$ 6.6 billion). The highest per capita cost was estimated for Puerto Rico, US$ 2764–4949 and the lowest for Peru US$ 445–821 (S2).

On average, the annual cost of treating one case was between US$ 1088 and US$ 1818. Countries of LAC expended in health an average of US$ 1063, with the highest among reported by Cuba (US$ 2280) and the lowest by Guyana (US$ 361). On average, NHE were notably lower among low income countries (US$ 508 per capita) and the highest among higher income countries (US$ 1063). Average expending on diabetes was close to average NHE for S1 and notably higher for S2. On average, among lower–middle income countries, NHE (US$ 508) was notably lower than the per capita cost of care for people with diabetes assuming either S1 (US$ 1014) or S2 (US$ 1832)

Table 5. The cost (US$×10⁶) of diabetes complications in Latin America and the Caribbean, 2015

Cost	Latin America		English Caribbean		Total	
	S1	S2	S1	S2	S1	S2
Cost of retinopathy	3345	6097	166	347	3511	6444
Cost of cardiovascular disease	5435	7870	235	396	5670	8266
Cost of nephropathy	2755	4434	147	258	2902	4692
Cost of neuropathy	2028	3560	107	208	2134	3768
Cost of peripheral vascular disease	1949	3686	90	1891	2040	3418
Total cost of complications	15511	25204	746	1384	16257	26588

Table 6. Total and per capita direct cost of diabetes mellitus (DM) and national health expenditures by country and GDP group, Latin America and the Caribbean, 2015

Lower–middle Income	National Health Expenditures (US$)	S1 (Lower)		S2 (Higher)	
		Direct costs (US$×10⁶)	Per capita costs (US$)	Direct costs (US$×10⁶)	Per capita costs (US$)
Bolivia	420	263.4	677	483.8	1244
El Salvador	565	353.2	1084	665.0	2040
Guatemala	462	1054.3	1385	1943.1	2552
Guyana	361	26.9	540	44.9	901
Honduras	428	464.4	1388	855.9	2559
Nicaragua	445	301.1	1091	512.0	1856
Paraguay	874	301.8	931	542.0	1673
Sub–total	508†	2765.1	1014†	5046.7	1832†
Upper–middle income:					
Argentina	862	1741.1	1010	3026.3	1756
Belize	487	20.9	728	32.5	1133
Brazil	1318	17492.5	1227	23825.7	1672
Colombia	962	2928.3	961	5367.5	1761
Costa Rica	1390	292.1	1047	521.6	1870
Cuba	2280	562.4	551	937.7	919
Dominican Republic	581	317.2	627	470.6	930
Ecuador	1042	1144.8	1379	1753.1	2112
Grenada	758	4.0	580	6.6	957
Jamaica	476	311.7	1538	509.3	2513
Mexico	1091	10659.1	930	14246.8	1243
Panama	1678	361.7	1568	605.8	2627
Peru	656	560.7	455	1010.7	821
Saint Lucia	721	8.3	625	13.9	1044
Suriname	947	26.2	625	41.9	1001
Venezuela	950	1773.6	831	2865.3	1343
Sub–total	1012†	38204.6	918†	55235.3	1481†
Higher–income:					
Bahamas	1818	48.5	1345		2021
Barbados	1198	31.7	928	50.8	1487
Chile	1717	1354.9	987	2054.2	1496
Puerto Rico*		1009.1	2764	1806.6	4949
Trinidad & Tobago	1822	190.2	1356	289.4	2063
Uruguay	1792	97.4	618	129.4	821
Sub–total	1669†	2731.8	1333†	4403.3	2140†
Total	1063†	43701.5	1088†	64685.3	1818†

* National Health Expenditures (NHE) figure for Puerto Rico was not available.

†Average.

The total cost of diabetes in LAC was estimated to be between US$ 103 and US$ 124 billion in 2015. The highest cost was estimated for Brazil between US$ 37 and US$ 43 billion while the lowest cost was estimated for Grenada between US$ 39 and US$ 42 million (**Table 7**).

Table 8 presents a summary of detailed explanations of all components, sources of the data, estimations and the corresponding cost result.

DISCUSSION

The estimated number of people with DM in countries of LAC soared from 15 million in 2000 to 41 million in 2015, – a 2.7–fold increase in 15 years. In 2015, the economic burden of diabetes was estimated to be between US$ 103 and US$ 124 billion, which represents a 6 to 7–fold increase in the total cost, 4 to 6–fold increase in direct medical, as well as a 8–fold increase in indirect costs compared to the previously estimated costs for 2000 [1].

Data presented here tends to be conservative and may underestimate the real cost of diabetes. This analysis included the best information available, however, there is a lack of information on the cost of proce-

Table 7. Direct, indirect and total cost of diabetes mellitus (DM) by country and GDP, Latin America and the Caribbean, 2015

Lower–middle income:	Indirect costs (US$×10⁶)	S1 (Lower)		S2 (Higher)	
		Direct costs (US$×10⁶)	Total costs (US$×10⁶)	Direct costs (US$×10⁶)	Total costs (US$×10⁶)
Bolivia	358	264	622	485	843
El Salvador	245	355	601	667	912
Guatemala	523	1059	1582	1948	2471
Guyana	44	28	72	46	90
Honduras	180	467	648	859	1039
Nicaragua	110	307	417	518	628
Paraguay	229	305	534	546	774
Sub–total	1690	2786	4476	5068	6757
Upper–middle income:					
Argentina	1740	1771	3511	3057	4796
Belize	21	22	42	33	54
Brazil	19052	18271	37323	24605	43656
Colombia	2805	3087	5892	5527	8331
Costa Rica	286	298	584	527	814
Cuba	1590	581	2170	956	2545
Dominican Republic	464	328	792	481	946
Ecuador	742	1187	1929	1795	2537
Grenada	35	4	39	7	42
Jamaica	239	328	567	526	765
Mexico	17240	10835	28075	14423	31663
Panama	344	364	708	608	952
Peru	1209	571	1780	1021	2230
Saint Lucia	11	9	20	14	26
Suriname	51	27	78	43	94
Venezuela	6062	1800	7862	2891	8953
Sub–total	51890	39483	91373	56514	108404
Higher–income:					
Bahamas	70	50	120	75	145
Barbados	40	33	73	52	92
Chile	2224	1430	3654	2129	4353
Puerto Rico	440	1035	1475	1832	2272
Trinidad & Tobago	315	199	514	298	613
Uruguay	512	105	617	137	649
Sub–total	3601	2852	6453	4523	8125
Total	57181	45121	102302	66105	123286

dures and services. Therefore, these costs were not included in the amount attributed to consultations, emergency visits, hospitalizations or visits to ophthalmologists. On the other hand the frequency of testing and consultations, may vary widely among countries. The cost of medications and care might have variations depending on purchasing capacity and government policies. Because of that, two different scenarios were prepared. For S1 and S2, lower and higher coverage for medication, testing and service as well as cost for treating diabetes complications respectively were assumed. These different estimates resulted in very different direct cost estimates for scenario 1 and scenario 2. Keeping constant indirect costs, the observed variation of the total cost of diabetes reflects the sensitivity to different assumption for each component such as medication and care for complications. Scenario 2 is 31 percent costlier than scenario 1. Sensitivity is also clearly related to the cost of medication. For example If all other cost assumptions are kept as established for S1 and S2, and the cost of insulin is reduced to US$ 4.20 per vial, it would result in cutting direct cost in 50% and the per capita cost of diabetes care by 35% (data not shown).

The proportion of direct and indirect cost was 44% and 56% for S2 and 54% and 46% for S1 respectively. These variations are driven by the difference in access to care and the cost of complications assumed for S1 and S2. These results are consistent with previous research, for example, an African study calculated direct medical cost at 43% and indirect cost at 56% [25] similar to our proportion in S1; while the ADA estimates indicated a higher proportion of direct cost at 72% and lower proportion of indirect cost

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Table 8. The cost of diabetes in Latin American and the Caribbean in 2015

INDIRECT COST	SOURCE	COST (US$)
Number of people with DM	41 576 396. Estimated by the Diabetes Atlas	
Permanent disability	Number of persons with diabetes with permanent disability: 1 043 128. Estimated by multiplying the economically active diabetes population in each country by the proportion of people with permanent disability by age and gender. These proportions were calculated by estimating the proportion of people receiving benefits due to diabetes by age and gender in Brazil, adjusted by diabetes duration and the prevalence of chronic disabling diabetes complication in the Chilean database (those with amputations, Chronic Kidney Disease (CKD), blindness, cerebrovascular disease and infarctions), approximate 33.5% of the total population with diabetes.	
	Cost calculated by multiplying years lost to disability by annual country GNP per capita. Cost of permanent disability in one year.	16 204 846 613
Temporary disability	The estimated number of person with diabetes in the labor force was estimated by discounting the unemployed (according to each country unemployment rate published by the World Bank) among those in working ages (20–64 y of age): 31 872 702. Number of sick days related to diabetes 10.5 days per person per year as per results of the ViCen survey.	
	Number of years lost due sick days: 858 154. Cost calculated by multiplying years of productivity lost by GNP per capita.	13 391 123 563
Mortality	Estimated number of all causes deaths: 1 386 513.	
	Calculated by the Population Attributable Fraction using OR obtained from the BES study.	
	Estimated number of deaths among those with diabetes: 318 102 (173 532–461 789).	
	Estimated number of years lost due to premature mortality: 2 074 633. Years lost before age 65 y with a 3% discount rate. Cost calculated by multiplying years lost to premature mortality in each country by annual GNP per capita.	27 585 053 690
Indirect cost total		57 181 023 866
Direct cost		
Insulin	Scenario 1: Proportion of people with diabetes using insulin: 10%.	
	Insulin consumption per year: 10 000 units per person	
	Number of insulin users: 4 053 699. Cost of insulin in each country obtained from the PAHO database.	66 995 221 314
	Scenario 2: Proportion of people with diabetes using insulin: 20%.	
	Insulin consumption per year: 10 000 units per person	
	Number of insulin users: 6 914 458. Cost of insulin in each country obtained from the PAHO database.	11 611 301 234
Oral medication	Scenario 1: Oral medication consumption per year: 1500 tablets of Metformin. Users 50% of the diabetes population	
	Oral medication users: 19 748 788. Cost of metformin in each country obtained from the PAHO database.	44 028 574 000
	Scenario 2: Oral medication consumption per year: 1500 tablets of Metformin. Users 80% of the diabetes population	
	Oral medication users: 33 572 940. Cost of metformin in each country obtained from the PAHO database.	6 848 575 800
Consultations	Scenario 1: Estimated that 50% of people were followed by health services.	5 067 964 481
	Estimated number of consultations related to DM per year for people with diabetes: 105 312 278. Number of consultations per inhabitant from PAHO's basic indicators. The ViCen survey indicated that people with diabetes had 3.5 more visits than those without diabetes. Visit for general causes were subtracted. The number of consultations due to diabetes was multiplied by the estimated number of people with diabetes in each country. The cost of consultations per country was obtained from the PAHO database.	
	Scenario 2: Estimated that 85% of people were followed by health services. Estimated number of consultations related to DM per year for people with diabetes: 162 755. Number of consultations per inhabitant from PAHO's basic indicators. The ViCen survey indicated that people with diabetes had 3.5 more visits than those without diabetes. Visit for general causes were subtracted. The number of consultations due to diabetes was multiplied by the estimated number of people with diabetes in each country. The cost of consultations per country was obtained from the PAHO database.	6 805 773 280
Hospitalizations	Scenario 1–2: Total number of DM hospitalizations per year for people with diabetes: 18 293 614. The ViCen survey indicated that people with diabetes were hospitalized 7 times and hospital stay was 1.9 d longer than those without diabetes. Number of hospital discharges per inhabitant for the general population from the PAHO basic indicator database was used to estimate the excess hospital days due to diabetes in each country. Cost of one hospital day in each country obtained from the PAHO database.	10 333 828 105
Emergency visits	Scenario 1–2: Total number of DM emergency visit per year for people with diabetes: 95 625 710; estimated number of diabetes related emergency visits 95 626. The ViCen survey indicated that people with diabetes had 1.4 more emergency visit than those without diabetes.	11 058 606 746
	Number of emergency visits per inhabitant for the general population from the PAHO basic indicator database was used to estimate the excess emergency visits due to diabetes in each country. Only visits assumed to be related to diabetes were included in cost calculation. Cost of an emergency visit in each country obtained from the PAHO database.	
Test and laboratory exams	Scenario 1: Includes the cost of one A1c, one lipid profile, one albuminuria test, one EKG, and one X Ray for 50% of the diabetes population of each country. Cost of items in each country obtained from the PAHO database.	1 379 772 482
	Scenario 2: Includes the cost of three A1c, one lipid profile, one albuminuria test, one EKG, and one X Ray for 50% of the diabetes population of each country. Cost of items in each country obtained from the PAHO database.	2 858 452 553

Table 8. Continued

Indirect cost	Source	Cost (US$)
Excess cost of complications	Scenario 1: The age–and–gender weighted probability of diabetes complications (cardiovascular disease 0.11, nephropathy 0.06, neuropathy 0.09, peripheral vascular disease 0.06 and retinopathy 0.12) was obtained from the Chilean QUALIDIAB database. The excess cost of each diabetes complication was applied to the cost of uncomplicated cases following results from the Mexican NIH database (excess cost of complications: neuropathy 1.08; peripheral vascular disease 11.06; cardiovascular disease 1.23; nephropathy 11.76; retinopathy 1.09)	16 256 804 668
	Scenario 2: The age–and–gender weighted probability of diabetes complications (cardiovascular disease 0.11, nephropathy 0.06, neuropathy 0.09, peripheral vascular disease 0.06 and retinopathy 0.12) was obtained from the Chilean QUALIDIAB database. The excess cost of each diabetes complication was applied to the cost of uncomplicated cases following results from the Mexican NIH database (excess cost of complications: neuropathy 1.58; peripheral vascular disease 1.81; cardiovascular disease 1.86; nephropathy 2.96; retinopathy 1.86)	26 587 999 416
Direct cost total	Scenario 1	45 120 771 799
	Scenario 2	66 104 537 136
Total Cost of DM	Scenario 1	102 301 795 665
	Scenario 2	123 285 561 002

DM – diabetes mellitus, y – year

at 28% [26] because of the well–known high cost of many medical services and procedures in the United States. The Brazilian study estimated the direct and indirect cost at 63% and 37%, respectively [17]. But the difference in the proportion of direct and indirect cost can be also due to the inclusion of different items in the study, real differences in the cost of procedures and medications, as well as differences in access to care.

On average, health care cost was estimated at US$ 1088–1819 per capita with wide ranges from US$ 4979 (S2) in Puerto Rico to US$ 540 (S1) in Guyana. The ADA [26] study estimated the per capita cost of diabetes at US$ 7900 [21] in the US, which was much higher than the cost reported in this study for LAC. In Africa, this figure varied from US$ 2144.3 to US$ 11 431.6 depending on the country's Gross National Income [25]. Interestingly, there were substantial differences in the items included in the North American, African and this current LAC study. The ADA [26] and the African [25] studies both included diabetes supplies, in addition the ADA [26] study included home care; those items were not included in the present study.

Our results for per capita direct cost was consistent to previous research in the region such as those published for Brazil [17], Argentina [27], and the South–Central America (SACA) Region [27]. The Brazilian study estimated the direct per capita cost to be US$ 1334 [17], which is close to the US$ 1227–1 672 we estimated for Brazilian persons with diabetes. The Argentine study [27] estimated the quarterly direct per capita cost of DM in a social security institution at US$ 904.60 and US$ 1841.80 Argentine pesos for DM cases with and without chronic complications, respectively. These figures translate into US$ 1796.82 (without chronic complications) and US$ 2037.89 (with chronic complications) per year. These estimations are closed to estimations reported in this study for Argentina (US$ 1010–1773) [27]. De Rocha Fernandes et al. [28] calculated health care cost for the IDF–SACA region between US$ 1155 and US$ 2024 for 2014, which overlap to our results for the same region of IDF at US$ 1136–1711 (data not shown).

A big gap was observed between NHE and the cost of diabetes care especially among lower income countries. This gap, as suggested by Arredondo et al [29] in Mexico, may result in out of pocket expenses in some cases [25] or the avoidance of necessary services because of economic constrains in others.

The total economic burden of diabetes among countries is highly driven by the size of the population, baring higher cost for countries with bigger population size such as Brazil, Mexico and Argentina. Per capita direct cost however, depends more on national prices of goods and services. Some of them have proven to be highly variable. The best example is the price of a vial of insulin, which price varied from US$ 78 in Puerto Rico to US$ 1.25 in Cuba (average price US$ 20). The Pan American Health Organization Strategy Fund (PAHO–SF) offers high quality medicine at affordable prices to countries of the Americas [30]. For example, a vial of 100 ml of high quality insulin is offered by PAHO–SF at US$ 4.20 to Member States. Running our analysis replacing country specific prices for insulin and oral medication with PAHO–SF's prices (plus 15%) in our data, resulted in cutting direct cost in 50% and the per capita cost of diabetes care by 35% (data not shown).

Prevalence estimates in this paper are based on epidemiological studies on the frequency of DM prepared for the Diabetes Atlas [2]. It was assumed that 55% (S1) or 85% (S2) of the total number of cases received care; however, this proportion may vary widely from country to country. Furthermore, the proportion of cases receiving treatment may vary according to access to care, patient's educational level, and the capacity of the health system.
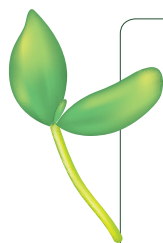
Major limitations of this study include the lack of information on many issues which were replaced by assumptions that in many cases cannot be confirmed. That is the case of the proportion of cases receiving services, the prevalence of diabetes chronic complications (approximations are based on one local study), and the proportion of people with permanent or temporary disability. In every case the best information available was used to generate estimates for the missing information. The results of this study were consistent when compared, as discussed previously, to small number of research reports available in the medical literature on the subject from Argentina [27], Brazil [17] and the SACA Region [28]. It is, however, suggested that these results be considered with caution, since inaccuracy may occur when making similar assumption for many countries with different health and financial systems. All cost components were adjusted to the age–and–sex population estimates for each country, except for the proportion of cases receiving treatment or under care. The latest was not possible because of the lack of information on these issues. Finally, we used in our estimates commercial prices for services and medication for each country. This was done so because prices for government provided goods and services were not available in every country. It may be possible that these services and medications are available at lower subsidized prices in some of the countries. Prices of medication and services for each country depended on information provided by a wide variety of collaborators including government officials, member of diabetes or professional associations, health providers and other volunteers. Biases introduced by the observers could not be controlled in any possible way.

While providing comparable estimates of the cost of diabetes among countries, this paper alerts public health officials of the growing burden of DM in LAC. It provides arguments to reinforce needs to strengthen public policies that promotes health and diabetes prevention, such as those that discourage the consumption of junk food or sugary drinks and promote physical activity; as well as those focused on increasing access to diabetes care and supplies.

DM represents a major public health problem in LAC. Middle and low–income countries face a major challenge that not only affects their health system organization and financing, but also their economic growth. Buying medication from PAHO–SF instead of paying market prices may reduce the burden that diabetes care represents to countries and individuals. As the prevalence of DM is expected to increase in the near future, so will its toll on individuals, families and society as a whole.

CONCLUSIONS

The high economic burden of diabetes showed here has strong implications for the health systems and the economic grow of the nations of LAC. This burden is related to direct medical care but also to indirect cost caused by loss of productivity due to premature death and disability. Multi–sector public policies could contribute to curve this treat on the long term.

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Causes of death among women aged 17–49 years between 2007 and 2010 in Maputo, Mozambique

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Objectives To describe causes of death among young women and estimate the role of HIV/AIDS as a cause in Maputo City, based on the civil death register.

Methods Death data of 17–49 year–old women were abstracted from January 2007–March 2010 from the civil death register in Maputo City, registering overall about 15 000 deaths per–year. Causes of death in the register were either based on physicians' diagnoses on death certificates or determined by asking questions to deceased relatives. Causes of death were written in Portuguese; we translated them into English and classified them into 106 codes using ICD–9; these codes were then categorized into 10 groups. Estimated populations from the 2007 census were used to calculate annual mortality rates. An earlier study was used to compare deaths in 2001.

Findings A total of 9640 deaths (6510 for residents of Maputo City) were registered and 77% had a specified cause of death reported. HIV–deaths represented 36% of all deaths and 40% among 25–39 year–olds. The death rate did not increase linearly by age, as there was a peak among women aged 30–34 years. The overall annual death rate was 6.7 deaths per 1000 population, with a notable decline by year. Death rates for HIV slightly declined by year. HIV–deaths explained most of the peak in death rate among 30–34–year–olds. The share of HIV–deaths among all deaths increased from 18% in 2001 to 35% in 2007–2010. Sixty–eight percent of all and 92% of HIV–related deaths occurred in hospital, with no increase over time.

Conclusions Routine death register was useful to study death rates, distribution of deaths, and change over time in the urban setting of Maputo during late 2000s. Over time, the death rate among 17–49 years old women seemed to have declined, but the relative contribution of HIV increased.

Available data from various sources in Sub–Saharan Africa show that in recent decades the overall death rate has declined and the distribution of causes of deaths has changed [1,2]. Chronic diseases and violent deaths (especially traffic accidents) have partly replaced infectious diseases. However, the HIV epidemic appears to have slowed the mortality decline and increased the role of infectious diseases [1,2]. Most conclusions on death rates and causes are based on estimates derived from censuses and ad hoc studies, as death registration is incomplete or content unreliable [1–3]. With the exception of South Africa, there are few studies on causes of death using civil death registration systems [4–7].

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Maputo City in Mozambique has a death registration system, but the data have been used sparingly for health statistics or research. There is one study [8] from 1994 and another published as an internal report in 2001 [9]. The first purpose of this study was to describe the recorded causes of death among 17–49 year–old women in Maputo City in 2007–2010 using the civil death registration system. Second, we aimed to estimate the role of HIV/AIDS as a cause of death. Furthermore, we estimated overall death rates, calculated the proportion of deaths occurring in hospital, and compared the causes of deaths to those reported in a 2001 study [9]. The data are a spin–off from a trial [10], for which the outcomes of the study women were searched from various sources.

CONTEXT

Mozambique is a low income country in Sub–Saharan Africa. After the end of the long civil war in 1992, Mozambique's economic development gradually recovered, and the health of the population improved, with the exception of a severe HIV epidemic. In 2010 national estimates of HIV–prevalence among 15–49 year–olds were 13.8% and among pregnant women 15.8% [11]. However, UNAIDS–adjusted estimates for adults, taking into account the population structure, were somewhat lower (11% in 2011) [12].

Maputo City is the capital of Mozambique, located in the southern region with more than one million residents. In Maputo, societal and health indicators are notably better than in the rest of Mozambique. In 2012, the GDP per capita was almost double that of the average national level (US$ 1 153 vs 593) and illiteracy rate was only 6% vs 33% nationally [13]. Due to the civil war, Maputo was isolated from the rest of the country until 1992; as a consequence HIV arrived there late [8], but it spread rapidly. It has been estimated that in the whole southern region (including Maputo) the prevalence of HIV in 2010 among 15–49 year–old women was 21% [14]. In Maputo, in a cohort of pregnant women in 2006–2008 recruited into a pragmatic randomized controlled trial on iron prophylaxis in Maputo, the HIV–positivity was 20% [10].

At the time of the iron study, pregnant women in Maputo were eligible for and utilized prenatal care (unpublished data from local experts), and HIV testing was routinely offered the whole country [15]. In Mozambique, the guideline on the organization of HIV–treatment was revised during the years of the study [12,16]. To our knowledge, HIV–positive women were given antiretroviral drugs in some Maputo prenatal centers, but not in other prenatal centers (unpublished data from local experts). It has been estimated that in the southern region the coverage of prevention of mother to child transmission of HIV was 73% in 2010 [14]. Outside pregnancy, HIV–testing was self–initiated and antiretroviral drug treatment was available through designated clinics.

METHODS

Originally the death data were collected to complete the tracing of 4326 pregnant women recruited for a trial in Maputo [10]. In that trial, the effects of two iron administration policies (routine iron prophylaxis vs screening and treatment for anemia during pregnancy) on maternal and child health were compared. The results from the trial have been presented in a previous paper [10].

Ethical approval for the study was obtained from the Mozambique Ministry of Health Ethics Committee (CNBS [Ref. 84/CNBS/06]) and Eduardo Mondlane University Medical Faculty Ethics Board (Jan 25, 2006) [10]. A positive statement was obtained from the National Research and Development Centre for Welfare and Health (STAKES), Helsinki, Finland (Dno 2571/501/2007). Oral and written informed consent was obtained from participating women [10].

The deaths of all 17–49 year–old women registered in the Maputo City civil death register (Registo Civil) from January 2007 to March 2010 were included in the study. The death registration system in Maputo is described in **Online Supplementary Document.** In brief, there was only one civil death register (Registo Civil) in Maputo City, registering overall about 15 000 deaths per year. Deaths were registered by the location of death, and many deaths of people from nearby areas were registered in Maputo City. If the death occurred at home, relatives reported it to a civil administrative office, where a letter of declaration of death was written. The relatives took the letter to the Registo Civil office, where a death report was written and a death certificate issued. If the death occurred in a health facility, the death certificate was filled in by a physician. The death certificate was taken to the Registo Civil by the relatives or a person from the Registo Civil located in a mortuary or in hospital. In the Registo Civil death reports were first

piled as loose papers and later compiled into books. All documents were handwritten (**Online Supplementary Document**).

The cause of death was reported in death reports (**Online Supplementary Document**). In the case of a hospital death a physician wrote the cause on the death certificate, and the Registo Civil official copied it into the death report. If the deceased relatives had no death certificate, the Registo Civil official asked certain questions to elicit the causes of death.

For this study we collected the following information from the death reports in Registo Civil: register number, age, date of birth, residence, date of death, place of death (hospital/out of hospital), date of death registration, basic cause of death (written in Portuguese or a local abbreviation code). Data were then entered by hand on data collection sheets, and later computerized into Microsoft Access 2000 database. We did not verify the causes of death, but took the information as noted in the death register.

Classification of causes of deaths

Causes of deaths were hand written in Portuguese, either as diagnoses, lay terms or by local abbreviation codes. The different terms (about 1000 and 534 when similar terms were combined) were translated into English (a Finnish researcher with nursing background, fluent in both Portuguese and English, SP).

The English terms and the local abbreviation codes were classified using the 9th version of the International Classification of Diseases and Related Health Problems (ICD–9 codes) into 106 codes. The coding was made by a physician (EH), discussing with other researchers. The most common abbreviations were clarified by the local researchers. The ICD codes were grouped into 18 and 10 groups (see Results) to reflect the likely cause of death, taking into account the inaccuracy at the registration stage. Mostly only one cause of death was given. In a few cases two causes were given, eg, HIV and tuberculosis. In that particular case, we classified the cause as HIV. All classifications were made solely on the basis of the causes of death and women's background characteristics were not used in the coding process.

Statistical analysis

For analysis, the data in Microsoft Access 2000 format was transformed into SPSS. Cross–tabulations of the grouped causes of deaths were made by age and year, and the proportions of HIV deaths were calculated. In the 2007 death register books, 12 women died in 2006: they were included in the total deaths, but excluded from yearly data. Maputo City residents were defined by the information in the Register.

To calculate annual mortality rates for Maputo City residents, the projected population numbers from the Instituto Nacional de Estatistica (INE) were used [17]. The INE used 2007 census numbers to make projections for the coming 40 years. The projected numbers were given by 5–year age groups, sex and province, separating Maputo City, as Maputo City is informally treated as an independent province. We calculated the total death rates (per 1000 population) across age groups by dividing the total number of deaths by the population size of each age group. Similarly, HIV–related death rates (per 1000 population) were calculated across age groups by dividing the number of HIV–related deaths by the population size of each corresponding age group. We calculated the confidence interval for the death rates using the Wilson score method [18].

At the time of the data collection, death data for 2010 was available for the first three months of the year. For calculating the annual HIV–related death rates for 2010, we multiplied the death rate by four. As some deaths, particularly malaria, are sensitive to the time of year, the 2010 results are given with reservation (see Results).

To compare our results to those reported in 2001 we relied on a table describing deaths of 15–44 year–old women, who had been registered in the Maputo City death register [9]. To make our study population more similar to the 2001 population, women aged 45–49 were excluded. The grouping of causes of deaths was modified so that it matches the grouping used in the 2001 study, which was based on the Burden of Disease Study categories [9].

RESULTS

Altogether 9643 deaths among 17–49 year–old women were recorded in the Maputo City death register, of whom 6513 were Maputo residents. Three women aged less than 17 years were excluded, leaving 6510 women.

The causes of death categorized into 10 groups are given by age in **Table 1** and in more detail in Table S1 in **Online Supplementary Document**. Most deaths had a cause registered and only in 0.5% of deaths was the cause lacking. But in 22% of deaths the cause was ill–defined or we could not translate it into a disease class. HIV–related deaths represented over a third of deaths, being close to 40% among 25–39 year–old women. Tuberculosis was recorded as the cause of death in 8%, malaria in 5% and other infections in 8% of women. Chronic diseases represented 12% of deaths, but their share increased notably by age. Violent (non–disease) deaths represented about 2% of deaths (5% among the youngest age group, 17–24 year–olds), and more than half of them were due to intentional violence.

Table 2 gives the estimated death rates by age. The overall annual death rate was 6.7 deaths per 1000 population. The death rate did not increase linearly by age, as there was a peak among 30–34–year–old women. Only the oldest age group (45–49 year–old) had a higher death rate than the 30–34 year–old women. HIV–related deaths explained more than a third of the peak among the 30–34 year–old women.

Table 3 gives the estimated death rates by year. The overall death rate notably declined by year, from 7.2 per 1000 population in 2007 to 6.4 in 2009. The rate in 2010 covers only the first three months. HIV death rates also declined during the period (**Table 3**).

We also inspected the time–trends by age and year (Table S2 in **Online Supplementary Document**). In the two youngest age groups death rates declined over time, but in the older age groups the trends were not systematic. HIV–death rates declined in the three youngest age groups and among the 40–44–year–olds, but among the 35–39 and 45–49 year–olds there was a U–shaped trend.

Table 4 gives the distribution of deaths by the place of death, specifying HIV–deaths. In all years, most deaths (overall 92%) diagnosed as HIV–related, had occurred in a hospital. The proportion of other deaths occurring in hospital was only a little over half, with no increase over time. In each year the difference between HIV–deaths and other deaths is statistically significant ($P<0.001$).

Table 1. Distribution of deaths (%) by age and cause of death, 17–49 year–old women, Maputo residents, 2007 – March 2010

Death cause	Age group						
	17–24	25–29	30–34	35–39	40–44	45–49	Total
Total number of deaths	1061	1421	1371	1043	856	758	6510
HIV	317 (29.9)	551 (38.8)	556 (40.5)	407 (39.0)	272 (31.8)	219 (28.9)	2322 (35.7)
Tuberculosis	93 (8.8)	121 (8.5)	127 (9.3)	89 (8.5)	69 (8.1)	50 (6.6)	549 (8.4)
Malaria	72 (6.8)	69 (4.9)	77 (5.6)	41 (3.9)	46 (5.4)	38 (5.0)	343 (5.3)
Other infections	117 (11.0)	118 (8.3)	105 (7.7)	61 (5.8)	55 (6.4)	49 (6.5)	505 (7.8)
Anemia, malnutrition	36 (3.4)	57 (4.0)	43 (3.1)	30 (2.9)	28 (3.3)	27 (3.6)	221 (3.4)
Pregnancy related	35 (3.3)	42 (3.0)	26 (1.9)	20 (1.9)	18 (2.1)	6 (0.8)	147 (2.3)
Chronic diseases	115 (10.8)	113 (7.9)	126 (9.2)	129 (12.4)	142 (16.6)	164 (21.6)	789 (12.1)
Violent death	51 (4.8)	25 (1.8)	23 (1.7)	22 (2.1)	15 (1.7)	12 (1.6)	148 (2.3)
Not clear*	221 (20.8)	316 (22.2)	43 (3.1)	280 (20.4)	209 (24.4)	188 (24.8)	1453 (22.3)
No information†	4 (0.4)	9 (0.6)	26 (1.9)	8 (0.6)	2 (0.2)	5 (0.7)	33 (0.5)
Total %	100.0	100.0	100.0	100.0	100.0	100.0	100.0

*Ill–defined causes, unknown abbreviation.

†No cause of death.

Table 2. Estimated annual death rates by age, 17–49 year–old women, Maputo residents, 2007 – March 2010

	Age group						
	17–24	25–29	30–34	35–39	40–44	45–49	Total
Population in 2007–2010*	338 864	183 206	150 841	124 659	96 065	74 907	968 541
Number of deaths	1061	1421	1371	1043	856	758	6 510
Death rate per 1000 per year (95% CI)	3.13 (2.95–3.32)†	7.76 (7.36–8.17)	9.09 (8.62–9.58)	8.37 (7.88–8.89)	8.91 (8.34–9.52)	10.12 (9.43–10.86)	6.72 (6.56–6.89)
Number of HIV deaths	317	551	556	407	272	219	2 322
HIV death rate per 1000 per year (95% CI)	0.94 (0.84–1.04)†	3.01 (2.77–3.27)	3.69 (3.39–4.00)	3.26 (2.96–3.60)	2.83 (2.52–3.20)	2.92	2.39 (2.30–2.50)

CI – confidence interval

*Projected populations (women): sum of 2007, 2008, 2009 and a quarter of 2010 projected populations.

†15–24 year–old population×8/10.

Table 5 compares the proportions of selected causes of deaths in Maputo death register in 2001 and 2007–March 2010. The 2001 data concerns 15–44–year–olds and were obtained from a published report [9]. In 2007–2010, data for Maputo residents only are also shown. The selected causes of deaths covered a much higher proportion in 2001 (81%) than in 2007–10 (63%). The share of HIV as a cause of death had notably increased during this short time period (from 18% to 35%), and that of tuberculosis and particularly malaria declined. The information in 2007–10 was relatively similar whether the analysis included all registered deaths or only Maputo residents.

Table 3. Rates and proportions of deaths due to HIV, by year, 17–49 year–old women, Maputo residents*

	2007	2008	2009	2010†
Population	290 975	297 012	303 189	309 460
Total deaths, n	2081	2091	1938	1584
death rate per 1000 (95% CI)	7.15 (6.85–7.46)	7.04 (6.75–7.35)	6.39 (6.11–6.68)	5.12 (4.90–5.40)
HIV deaths, n	883	675	620	572
HIV deaths, % of deaths (95% CI)	42.4 (40.3–44.6)	32.3 (30.3–34.3)	32.0 (29.9–34.1)	36.1 (33.8–38.5)
HIV death rate per 1000 (95% CI)	3.03 (2.84–3.24)	2.27 (2.11–2.45)	2.04 (1.89–2.21)	1.85 (1.70–2.01)

CI – confidence interval

*23 deaths excluded from the analysis as their date of death was missing.

†In 2010 the numbers of deaths in the first three months were multiplied by 4. The numbers which may be sensitive to time of year are given in square parenthesis.

Table 4. Proportions (%) of HIV and other deaths by death place and year, 17–49 year–old women, Maputo residents*

	2007	2008	2009	2010†	Total
No. HIV deaths:	883	675	620	143	2 321
In hospital	92.0	92.9	91.0	93.7	92.1
Elsewhere	8.0	7.1	9.0	6.3	7.9
Total %	100.0	100.0	100.0	100.0	100.0
Other deaths:	1198	1416	1318	253	4185
In hospital	53.7	54.7	54.6	52.2	54.2
Elsewhere	46.3	45.3	45.4	47.8	45.8
Total %	100.0	100.0	100.0	100.0	100.0
No. total deaths:	2081	2091	1938	396	6506
In hospital	69.9	67.0	66.2	67.2	67.7
Elsewhere	30.1	33.0	33.7	32.8	32.3
Total %	100.0	100.0	100.0	100.0	100.0

*23 deaths excluded from the analysis as their date of death was missing

†First three months. In each year the difference between HIV–deaths and other deaths in regard to the place of death is statistically significant (P<0.001)

Table 5. Comparison of selected causes of deaths among 15–44 year–old women in 2001 in Maputo death register to those among 17–44 year–old women in Maputo death register in 2007 – March 2010 and to Maputo residents in 2007 – March 2010*

	2001 Death Register		2007–2010 Death Register†		2007–2010 residents†	
Causes of death	Number	%	Number	%	Number	%
HIV	370	17.7	3367	34.9	2322	35.6
Tuberculosis	355	17.0	820	8.5	550	8.4
Malaria	474	22.7	476	4.9	344	5.3
Diarrhea	88	4.2	196	2.0	113	1.7
Pneumonia	72	3.4	147	1.5	105	1.6
Meningitis/Brain infection	36	1.7	173	1.8	120	1.8
Anemia	120	5.7	319	3.3	221	3.4
Maternal causes/Pregnancy related	70	3.4	220	2.3	147	2.3
Hypertension	57	2.7	278	2.9	184	2.8
Traffic accidents	51	2.4	44	0.5	21	0.3
Total		81.0		62.7		63.4
Total deaths	2090	100.0	9637	100.0	6510	100.0

*Only causes with specific diagnosis in the denominator (excluding deaths with missing or ill–defined cause).

†First three months in 2010.

DISCUSSION

Our study in an urban setting, Maputo in Mozambique, showed that overall the death rate among 17–49–year–old women declined from 2007–2010, the highest death rate was among 30–34–year–olds, and HIV was recorded as the cause of death in over a third of deaths. HIV–deaths explained most of the decline over time and observed variation by age. Other infections were common causes among younger women, but among women older than 40 years, chronic diseases as causes of death became more prevalent. Comparison to an older study suggests that the role of HIV as the cause of death had increased from 2001.

Can the results be trusted?

There is no good estimate of the coverage of registering deaths in Maputo. In a study from 1994, the coverage was estimated to be 86% [8]. The coverage at the end of 2000s may be higher. A death certificate is needed to get a burial place in a cemetery. In the city, burial space outside cemeteries is scare. Furthermore, relatives need the death certificate to receive money for pension and other benefits.

The recorded cause of death could be obtained technically by studying the register, but did the recorded death represent the real cause? There is no published validity study available. Two thirds of deaths, and over 90% of those recorded as HIV–deaths, had occurred in hospital. In hospital deaths, health personnel, mainly physicians, were involved. However, for one third of deaths, civil servants without medical background, even though trained to elicit replies to questions, determined the cause from relatives' descriptions. The method of verbal autopsy, if well–performed, can be useful for determining causes of death [18,19]. Furthermore, the results look plausible: the death rate increased and chronic diseases became more prevalent by age.

In South–Africa it has been suggested that to avoid social problems physicians do not write HIV for the cause of death [5]. In the Maputo death register, a HIV–diagnosis was common and in addition various abbreviations, which were not transparent for the lay–person, such as ODV (outras doenças por virus, other viral diseases) were used to indicate HIV. Studies from South–Africa show both poor coverage and low accuracy of causes of death in the civil death registration system [5–7]. However, the death registration system in Maputo is very different to that in South Africa, and comparison is not very helpful.

A limitation of our study is that we had an incomplete data for 2010, therefore given seasonal variations across the year, our conclusion may not be applicable to the whole year. The 2001 study was used to compare our findings to an earlier time. Unlike our study the 2001 study included women 15–17 years of age. This small difference in the compared populations is unlikely to explain the large differences in causes of death between the two time periods.

Comments on result details

HIV–infection was classified as the cause in over a third of deaths. This may be an underestimate, as HIV could have been behind a number of other deaths. If other causes were reported in addition to HIV, we classified the death as HIV. It was, however, rare to have multiple diagnoses. In a 2007 study based on census interviews, causes of death in the previous year were enquired about using a verbal autopsy method [11]. In that study almost half of adults dying of HIV had also had tuberculosis, and most persons who had tuberculosis as the cause of death also had HIV.

The relative contribution of HIV–infection had increased from 2001. But as the source we used for 2001 did not give comparable population numbers, we do not know if rates of HIV deaths had increased and if so, to what extent. In the time–period 2007–2010 there was a declining death rate overall and specifically for HIV. Death rates did not vary linearly by age and the highest rate was among 30–34–year–old women. The variation by age may be due to varying infection prevalence in different age cohorts or varying rates of HIV treatment. The future trend of HIV deaths among Maputo women is difficult to predict. In a cohort of pregnant women in 2006–2008, the HIV–positivity was 20%, and the highest rate was among 25–29–year–olds (28%) [10].

About 3% of causes of death were classified as anemia and/or malnutrition; some of these deaths may have been due to malaria, HIV or other infections. In our study, 1.7% of deaths were classified to be due to diarrhea. This is much less than in the 2001 study (4.2%) [9] or in a 1994 study (8.8% among 15–59 old women) [8]. Among older women, chronic diseases were common. Violent deaths represented 2.3% of causes of death, which agrees with previous findings showing that violent deaths are much less com-

mon among women than men [2]. A high share of violent causes of deaths were intentional violence (interpersonal violence and suicides). Furthermore, it is likely to be an underestimate as unclear cases were coded as non–intentional.

In addition to the current study and the one in 2001 [9] we found one older study from 1994 using death register data [8]. In the 1994 study, among 15–59–year–old women the ten leading deaths included malaria (11%) tuberculosis (9.8%), violent deaths (8.8%), diarrheal diseases (8.8%), but not HIV; the authors discuss that HIV has been underreported. However, the prevalence study in prenatal clinics showed only 2.7% of pregnant women to be HIV–positive, much less than in 2008–2010. Therefore, it is very likely that the role of HIV as a cause of death has notably increased and that of other infections has decreased since 1994. The high proportion of violent deaths in 1994 may be related to the close proximity of the long civil war, which ended in 1992. In a previous study using verbal autopsy to identify maternal deaths in a small series of subjects, HIV accounted for a higher proportion (52%) of maternal deaths than our study [20].

Further research

There are lack of data on trends in mortality levels and causes of death in Sub–Saharan Africa. Data from civil registration could serve as a useful data source to capture time trends and differences between the population groups. Using a similar approach to that employed in this study in other places may provide better understanding of the trends of death and their causes across Sub–Saharan Africa.

Implications for practice

Computerizing data on civil registration of deaths would allow up–to–date surveillance and future projections. The basic data to be collected should be simple and easy for lay people to record. A written diagnosis should be retained and coding done afterwards. To calculate death rates, population numbers by residence should be readily available. Studies using death registration may stimulate improving death registration.

CONCLUSION

HIV–deaths represented 36% of all deaths. The overall death rate did not increase linearly by age, as there was a peak among women aged 30–34 years, explained by HIV–deaths. Over time the death rate among 17–49 years old women seemed to have declined, but the relative contribution of HIV increased. The routine death register was useful to study the death rates, distribution of causes of deaths, and change over time in the urban setting of Maputo during the late 2000s.

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Methods used in adaptation of health–related guidelines: A systematic survey

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Background Adaptation refers to the systematic approach for considering the endorsement or modification of recommendations produced in one setting for application in another as an alternative to de novo development.

Objective To describe and assess the methods used for adapting health–related guidelines published in peer–reviewed journals, and to assess the quality of the resulting adapted guidelines.

Methods We searched Medline and Embase up to June 2015. We assessed the method of adaptation, and the quality of included guidelines.

Results Seventy–two papers were eligible. Most adapted guidelines and their source guidelines were published by professional societies (71% and 68% respectively), and in high–income countries (83% and 85% respectively). Of the 57 adapted guidelines that reported any detail about adaptation method, 34 (60%) did not use a published adaptation method. The number (and percentage) of adapted guidelines fulfilling each of the ADAPTE steps ranged between 2 (4%) and 57 (100%). The quality of adapted guidelines was highest for the "scope and purpose" domain and lowest for the "editorial independence" domain (respective mean percentages of the maximum possible scores were 93% and 43%). The mean score for "rigor of development" was 57%.

Conclusion Most adapted guidelines published in peer–reviewed journals do not report using a published adaptation method, and their adaptation quality was variable.

Guideline adaptation provides an alternative to de novo guideline development by making the process more efficient and avoiding duplication of efforts. Given that guidelines produced in one setting may not be applicable to other settings, adaptation takes into account the cultural and organizational differences in the new setting to guarantee their applicability [1]. This requires a well–structured adaptation methodology that takes into consideration affordability and availability of resources and services that would allow contextualizing global guidelines to countries of varying levels of income [2].

A number of adaptation methodologies have been proposed, including the Systematic Guideline Review Method [3], Making GRADE the Irresistible Choice (MAGIC) [4], GRADE–ADOLOPMENT [5], and ADAPTE [1]. GRADE is short for Grading of Recommendations Assessment, Development and Evaluation [6]. ADAPTE is one of the earliest systematic frameworks to adapt guidelines to a local context [1]. The ADAPTE framework

consists of 24 steps in three main phases: (1) set–up (preparation), (2) adaptation and (3) finalization [7]. The evaluation of guideline adaptation has been recommended to ensure the reproducibility and efficiency of the methods in producing high quality guidelines [8].

In a recently conducted study, we systematically evaluated the reporting of processes employed in the national adaptation of World Health Organization (WHO) guidelines for Human Immunodeficiency Virus (HIV) and Tuberculosis [9]. We found that 32 out of 170 (19%) guideline adaptations reported their processes. It remains unclear to what extent these findings apply to fields other than HIV and tuberculosis, or to guideline adaptions published in the peer reviewed literature. This is particularly relevant as the adaptation methods used could affect the quality, trustworthiness and applicability of the adapted recommendations.

Our main objective was to describe and assess the methods used for adapting health–related guidelines published in peer–reviewed journals, and to assess the quality of the resulting adapted guidelines.

METHODS

Definitions

We adopted the WHO definition of guidelines as "systematically developed evidence–based statements which assist providers, recipients and other stakeholders to make informed decisions about appropriate health interventions" [10]. We considered the following definition of guideline adaptation that is based on the ones proposed by Fervers et al. [1] and by the GRADE–ADOLOPMENT methodology [5]: systematic approach for considering the endorsement or modification of recommendations produced in one setting for application in another as an alternative to de novo development.

Eligibility

We included documents meeting all the following eligibility criteria:
- Meet the above definition of guideline adaptation;
- Adaptations of specific health–related guidelines (e.g., management of asthma, screening mammography); and
- Published in any language;

We also acquired papers that the authors referred to when describing their adaptation methods, and considered them in the review process.

We excluded documents:
- Describing an adaptation methodology process but not an actual adaptation;
- Meeting abstracts;
- Restricted to implementation only (e.g., for clinical decision support);
- Reporting appraisals of Clinical Practice Guidelines (CPGs) for the purpose of adaptation; or
- Reporting only algorithms.

Search strategy

We used the OVID interface to search Medline and Embase databases. The period of the search was from January 2000 to June 2015. **Online Supplementary Document** provides the detailed search strategies for each database. Also, we searched the reference lists of relevant papers (eg, reviews on adaptation methods) identified in our search. We did not use any language restrictions.

Selection process

All reviewers underwent calibration exercises. They screened the same set of papers and received feedback on their performance. Then, teams of two reviewers independently screened abstracts and full texts of identified citations for potentially eligible guideline adaptations. Next, the review teams screened the full text of citations judged as potentially eligible by at least one of two reviewers using standardized screening forms. The two members compared their results and resolved disagreement by discussion or with the help of a third reviewer as needed. When excluding an adapted guideline, we recorded the reason for exclusion.

Data abstraction process

All reviewers underwent calibration exercises for data abstraction. Teams of two reviewers worked in duplicate and independently to abstract relevant information from the included adapted guidelines (except 122 non–English papers which were abstracted by only one person: 63 were in either French or Spanish in which one of the reviewers (RAA) was fluent, and 59 were translated using Google Translate). They used standardized online data abstraction forms on REDCap™ [11]. They compared results and resolved disagreements by discussion, or with the help of a third reviewer.

We abstracted the following characteristics from each included adapted guideline:

- Characteristics of the adapted guideline: name and year of publication, country, contributors to guideline adaptation (governmental body, WHO Headquarter, Regional or National offices, Not for Profit Organizations (NGOs), professional society, "expert panel"), guideline area, reporting of source guideline.
- Characteristics of the source guideline: number of source guidelines, name and year of publication, country, contributors to source guideline development (governmental body, WHO Headquarter, Regional or National offices, NGOs, and professional society, "expert panel").
- Other information: disclosure of conflicts of interest, and funding (reporting, source, and role).
- We classified income levels of countries (for both adapted and source guidelines) as per the World Bank classification into high, upper–middle, lower–middle and low income countries.

We also assessed whether the authors explicitly reported using an adaptation method. We considered the following options: ADAPTE or one of its variants, other published adaptation method, or an unpublished adaptation method.

Next, we wanted to explore the specific steps followed in the adaptation process. As we did not identify any validated or standardized tool, we decided to rely on the steps described in ADAPTE (**Table 1**) [7]. We chose ADAPTE because it is a well–structured tool, and represents the most widely used method for guideline adaptation. Thus, we abstracted information about the steps covered in the adaptation methodology from papers reporting on at least one element of the adaptation phase of the ADAPTE process

Table 1. Phases and steps of the ADAPTE process

PHASES	STEPS
Set–up phase	1. Establish an organizing committee
	2. Select a topic
	3. Check whether adaptation is feasible
	4. Identify skills and resources needed
	5. Complete set–up tasks
	6. Write protocol
Adaptation phase	7. Determine the health questions
	8. Search for guidelines and other relevant documentation
	9. Screen retrieved guidelines
	10. Reduce total number of guidelines if there are more than can be dealt with by the panel
	11. Assess guideline quality
	12. Assess guideline currency
	13. Assess guideline content
	14. Assess guideline consistency (search and selection of studies, links between evidence and recommendations)
	15. Assess acceptability/applicability of the recommendations
	16. Review assessments to aid in decision–making
	17. Select between guidelines and recommendations to create an adapted guideline
	18. Prepare a document that respects the needs of the end users and provides a detailed transparent explanation of the process
Finalization phase	19. External review by target users
	20. Consult with relevant endorsement bodies
	21. Consult with developers of source guidelines
	22. Acknowledge source documents
	23. Plan for aftercare of the adapted guideline
	24. Produce high quality final guideline

[7]. So, the purpose was not to assess compliance with ADAPTE. Rather, we used ADAPTE to identify standard steps in the adaptation approach.

To appraise the quality of adapted guidelines, we used the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [12]. This tool was designed to assess the quality of guidelines by evaluating the rigor of guidelines development and transparency in reporting its processes. It is a 23–item tool, in which the items are distributed into six quality domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence (**Online Supplementary Document** provides a listing of the tool's 23 items and a description of its domains). The items in each domain are rated on a 7–point scale, where 1 indicates 'Strongly Disagree' and 7 indicates 'Strongly Agree'. We calculated the AGREE II "scaled domain score" for each domain, as suggested by the AGREE II group. For this, we added the scores of individual items of a particular domain, then we scaled the total score as a percentage of the maximum possible score in that domain [13]. The resulting scores of the six domains are independent and are not compared to a minimum score as recommended by the AGREE Consortium [12].

Data analysis

We conducted a descriptive analysis of all variables. We used frequencies and percentages for categorical variables. For continuous variables, we assessed the distribution for normality using the Kolmogorov-Smirnov test. For non–normally distributed variables, we used median and Inter–Quartile Range (IQR); otherwise we planned to use mean and standard deviation.

We used the Mann-Whitney test to assess the association between reporting (vs not reporting), the use of a published adaptation method and the quality of the adapted guideline, measured as the mean score for each AGREE II domain.

RESULTS

Study selection

Figure 1 shows the study flow. Out of a total of 12 021 captured citations, we identified a total of 72 eligible papers, each reporting on one guideline adaptation project. One of those (the Guideline of the Ger-
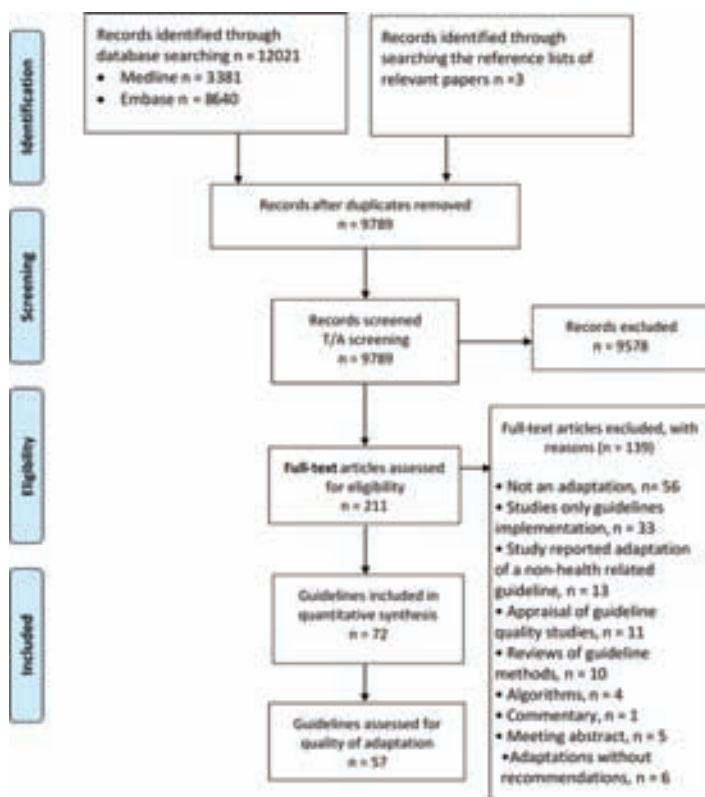
Figure 1. Study flow diagram.

man Society for Nutritional Medicine (DGEM)) included 13 different chapters in clinical nutrition but we considered them as one guideline. We excluded 139 papers based on full text screening for the following reasons: 56 were not related to adaptation, 33 were adaptations for implementation only, 13 reported adaptation of a non–health related guideline, 11 were appraisals for guideline quality, and 10 were review articles, 4 reported algorithms only, 5 were meeting abstracts, 6 were guideline adaptations without reporting of the resulting recommendations, and 1 was a guideline commentary.

Findings

Characteristics of the adapted guidelines

Table 2 provides a description of the 72 included adapted guidelines. Forty three percent (n = 31) of these adapted guidelines were published between the years 2012–2014. High–income countries produced 83% of the adaptations (n = 60), whereas lower–middle income countries produced only 6% (n = 4). Professional societies developed 71% (n = 51) of the adaptations, while governments were involved in only 11% (n = 8) of adapted guidelines.

The guideline development group reported conflicts of interests in 38 (53%) of the adapted guidelines. Forty seven percent of adaptations reported on the funding source. The most common funding sources were governmental in 15 (21%) adaptations, followed by private–for–profit organizations in 12 (17%) adaptations. Of the thirty–one adapted guidelines that reported being funded, only six reported on the role of the funder in the adaptation process. While three explicitly reported having no role, the other three reported being involved in: preparing the manuscript, employing an author, and covering costs of meetings.

Characteristics of the source guideline

Ninety percent of adapted guidelines reported on the source guideline (**Table 3**). The median number of source guidelines was 2.5 with an IQR of 4 (75th – 25th percentiles being 5 and 1). The IQR for the pub-

Table 2. Characteristics and setting of the adapted guideline (n = 72)

		No.	%
Publication year	Published 2012–2014	31	43
Country income	Low income	1	1
	Lower–middle income	4	6
	Upper–middle income	7	10
	High income	60	83
Guideline developer	Governmental body	8	11
	WHO regional/national	0	0
	Non–governmental organization (NGO)	1	1
	Professional society	51	71
	Other	12	22
Guideline area	Medical	62	86
	Surgical	5	7
	Psychiatry	3	4.2
	Other	5	6.9
Specifying source guideline		65	90
Disclosure of competing interests	Organizing committee/Guideline development group	34	48
	Panel members only	4	6
	Not reported	34	48
Funding	Not reported	38	53
	Reported as not funded	3	4
	Funded	31	43
Funding source	Internally funded	2	3
	Governmental	15	21
	Private–for–profit	12	17
	Private not for profit	4	6

Table 3. Characteristics of the source guideline (n = 72)

		No.	%
Country income	Low income	0	0
	Lower–middle income	2	3
	Upper–middle income	5	7
	High income	61	85
Developer	Governmental body	15	21
	WHO regional/national	9	13
	Non–governmental organization (NGO)	7	10
	Professional society	49	68
	Other	4	6

lication year of the source guidelines was 6 years (75th – 25th percentiles being 2010 and 2004). Eighty five percent of source guideline originated from high income countries. Most common source guideline developers were professional societies (68%), and WHO (13%).

Adaptation method (n = 57)

Out of 72 included papers, 57 reported at least one detail about the adaptation method. Of the 57 adapted guidelines that reported at least one detail of the adaptation method, sixty percent (n = 34) did not report using a published method for guideline adaptation. Forty percent (n = 23) reported using an adaptation method: either ADAPTE (n = 13); ADAPTE as modified by the authors (n = 3); or some other previously published method (n = 7), including: the Practice Guideline Evaluation and Adaptation Cycle (n = 4), the Systematic Guideline Review Method (SGR) (n = 1), RAND consensus method (n = 1), and Registered Nurses' Association of Ontario (RNAO) Toolkit for Implementation of Clinical Practice Guidelines (n = 1). As planned, we collected for these 57 papers information about the adaption method (ADAPTE steps) and the quality of the adapted guideline (AGREE II score).

ADAPTE steps

The total number of steps of ADAPTE reported to be followed by each of the 57 adapted guidelines ranged between 6 and 22 (out of a maximum value of 23). The median number was 14 and IQR was 4 (75th – 25th percentiles being 17 and 13).

Figure 2 show the number of adapted guidelines fulfilling each of the ADAPTE steps. The distribution (out of a maximum value of 57) ranged between 2 (4%) and 57 (100%). The median number was 38 and IQR was 27 (75th – 25th percentiles being 51 and 24). The percentages of guidelines fulfilling ADAPTE steps are presented in **Online Supplementary Document**.

At least 95% of the adapted guidelines met the first four steps of ADAPTE (ie, setup or preparatory phase). In the adaptation phase (steps 7 to 18), all adapted guidelines determined health questions, while 88% reported searching for guidelines or any other relevant documents. Only 16% of adapted guidelines assessed guideline consistency ie, assessment of the search and study selection, and links between evidence and recommendation. In the finalization phase: 91% acknowledged the source, but only 16% reported consulting with sources guideline developers.

Quality of the adapted guideline (AGREE II score):

Table 4 reports the AGREE II mean scaled domain scores for the 57 adapted guidelines. The mean scores were highest for the "scope and purpose" domain (93%) and "clarity of presentation" domain (86%). The mean scores were lowest for the two "applicability" and "editorial independence" domains (50% and 43% respectively). The mean score for "rigor of development" was 57%.

With regards to evaluating the association between reporting the use of a published adaptation method and the quality of the adapted guideline, we found a statistically significant association for the applicability domain but not for the scope and purpose, stakeholder involvement, rigor of development, clarity of presentation and editorial independence domains. For the applicability domain, the scores were 64% when reporting the use of a published adaptation method and 41% when not reporting such use ($P = 0.005$).
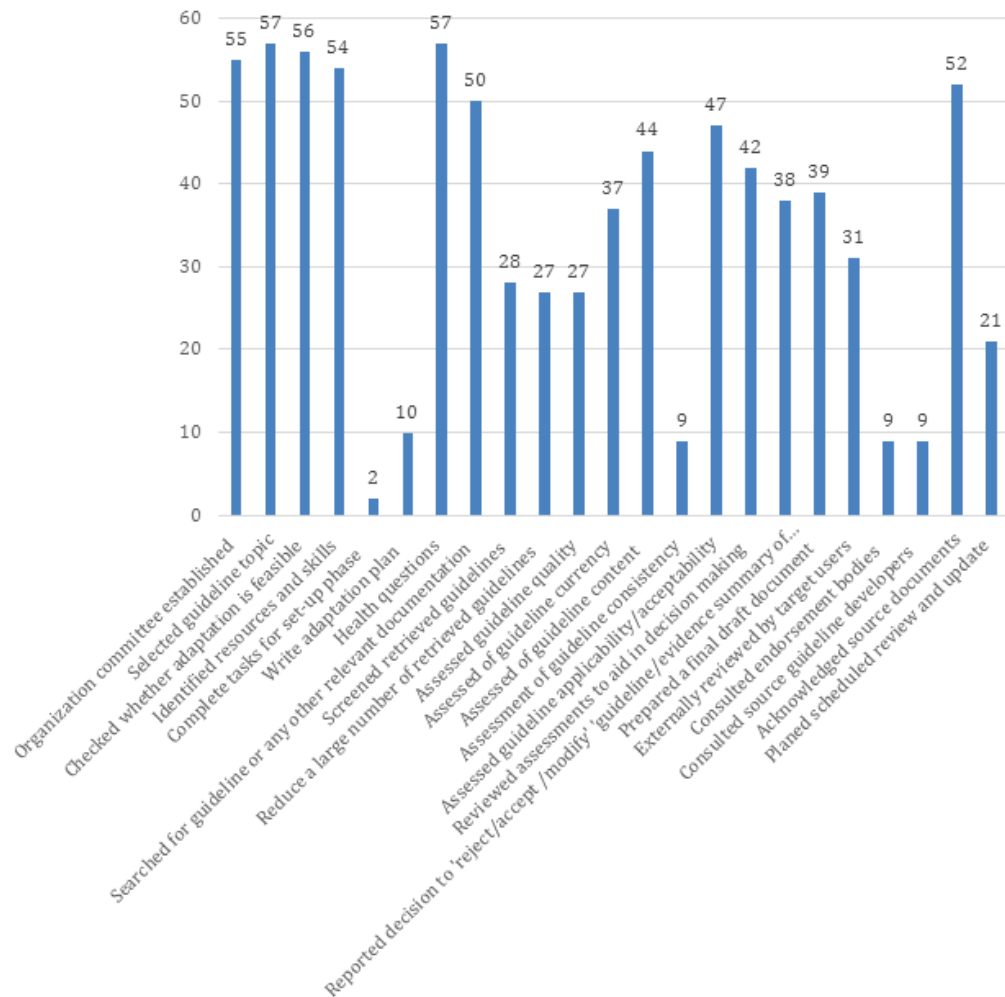
Figure 2. Number of ADAPTE steps fulfilled by adapted guidelines (n = 57).

Table 4. AGREE II mean scaled domain scores for adapted guidelines (n = 57)

Domain	Mean %	Standard deviation	Minimum%	Maximum%	95% confidence Interval
Domain 1: Scope and Purpose	93.37	10.09	55.56	100.00	90.69 to 96.05
Domain 2: Stakeholder Involvement	64.03	17.22	22.22	100.00	59.46 to 68.60
Domain 3: Rigor of Development	56.79	24.85	12.50	100.00	50.20 to 63.39
Domain 4: Clarity of Presentation	85.57	25.08	0	100.00	78.91 to 92.3
Domain 5: Applicability	50.14	28.85	0	100.00	42.48 to 57.80
Domain 6: Editorial Independence	42.54	34.88	0	100.00	33.28 to 51.80

DISCUSSION

Summary of findings

Our aim was to assess the methods used for adaptation and to assess the quality of health–related guideline adaptations. We identified 72 adapted guidelines published in the past 15 years through an electronic database search. Of the identified guidelines, the majority of both adapted guidelines and their source guidelines were published by professional societies, and in high–income countries. About a fifth of the adapted guidelines did not report any detail about their adaptation methodology. Of those that did, most did not use a published adaptation method. The ADAPTE framework was the most frequently used method but was used only in a quarter of the adapted guidelines. It is important to note that ADAPTE was developed and published after the publication of many of guidelines included in this study. The use of the different steps of guideline adaptation, as well as the quality of the guidelines was variable. A key step before adapting a guideline/recommendation should be an evaluation of how well the source guideline

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assessed, interpreted and made recommendations, but this may not be occurring. The use of a published adaptation method was associated with a higher score on applicability. This association suggests that the use of adaptation methodologies strengthens the relevance of the adapted guideline.

It is interesting that guideline adaptations are mostly published in high–income countries. It is very likely that adaptations of guidelines in low–income countries are not being reported in peer–reviewed journals, or are being reported in peer–reviewed journals that are not indexed. Capturing those guidelines would require searching governments' websites as well as national or regional journals.

Strengths and limitations

The main strength of this study is the use of standard systematic review methodology such as duplicate methods for guideline selection and data abstraction. Also, we used AGREE II instrument, a validated tool for assessment of guideline quality. While AGREE II was not specifically designed for adapted guidelines, we believe it still applies. While we used the ADAPTE steps to assess the process of guideline adaptation, the tool was actually developed for guiding the adaptation process and not for assessing it. Also, this tool was developed and published after the publication of many of adapted guidelines included in this study. Unfortunately, no tool for assessing the adaptation process is currently available. The main limitations relate to restricting the search to electronic databases, and not including adapted guidelines published only in governmental databases or websites, or published locally as reports.

Comparison to similar studies

We are not aware of any study that systematically evaluated the quality of adapted guidelines. Miguel–Garcia et al. assessed qualitatively the quality of the Spanish adaptation of the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice [14]. The authors highlighted the importance of considering clinical evidence both in developing the source guidelines and in adapting them. Alonso–Coello et al. systematically reviewed studies that used AGREE instrument to appraise guidelines in general (ie, not necessarily adapted guidelines). They found that, despite the fact that quality of guidelines improved over the last two decades, it remained moderate to low when measured with the AGREE instrument [15].

We are aware of two methodological surveys that systematically evaluated guideline adaptation process. Fervers et al. published a literature review in 2006 that identified 18 reports of models, practical examples and experiences of guideline adaptation [1]. They reported that none of these used a validated process for guidelines adaptation. Indeed, that paper was the basis for the ADAPTE framework [7]. Our team conducted the second survey that focused on adaptation of WHO guidelines for HIV and Tuberculosis, and also assessed the number of ADAPTE steps met by the adaptation processes on the national level [8]. The median number of ADAPTE steps in the study of WHO adapted guidelines was 11.5 [IQR = 3.5 (75th – 25th percentiles being 13.5 and 10)] compared to 14 [IQR = 4 (75th – 25th percentiles being 17 and 13)] in the current study. This lower number amongst WHO adapted guidelines was mainly related to lower values for the 'adaptation phase'. The difference could be related to the fact that guidelines assessed in the current study underwent peer review, which might have improved their reporting, or led to the selection of those with better processes.

Implications for practice

Guideline adaptation projects need to improve the reporting of their methods. This work suggests that when adapting guidelines, developers have either not evaluated the consistency of the source guideline (links between evidence and recommendation), or have not reported that they did. Increasing awareness of the different phases of adaptation, providing additional tools to facilitate evaluation, facilitating collaboration between developers, or making the evidence to recommendation process more transparent, may be warranted. Guideline adaptation developers also need to follow methodologies specifically designed for this purpose. For example, a large number of guidelines are currently using the GRADE methodology. Also certain adaption methodologies, eg, the "GRADE–ADOLOPMENT" framework encompasses adoption, adaptation and de novo guideline development. This process is building on newly–developed but also already published systematic reviews and health technology assessment reports. Another methodological advancement is the use of the GRADE EtD frameworks, which could facilitate the adaptation process [16].

Implications for future research

There is a need to develop a standardized tool for assessing the quality of conduct and of reporting of guideline adaptations, given that this methodology has features that are distinct from guideline develop-

ment. Such a tool would be helpful for both researchers in the field of guideline adaptation, and groups working on adapting guidelines. Also, research focusing on non–peer reviewed guidelines is needed to better assess methods used for adaptation efforts in low and middle–income countries (LMIC).

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The burden of respiratory syncytial virus (RSV) associated acute lower respiratory infections in children with Down syndrome: A systematic review and meta–analysis

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Background Acute lower respiratory tract infections (ALRIs) caused by respiratory syncytial virus (RSV) are a leading cause of hospitalization in infants. Numerous risk factors have been identified in the aetiology of severe RSV–associated ALRI necessitating hospitalisation, including prematurity and congenital heart disease. Down syndrome (DS), a common genetic disorder associated with congenital and dysmorphic features, has recently been identified as an independent risk factor for RSV–associated ALRI requiring hospitalisation; however, the disease burden of RSV–associated ALRI in this population has not yet been established. Similarly, the impact of DS as an independent risk factor has not yet been quantified. We aimed therefore to estimate the incidence of admissions in children with DS, and by comparing this with unaffected children, to quantify the risk of DS independent of other risk factors.

Methods A systematic review of the existing literature published between 1995 and March 1, 2017 was performed to quantify the incidence of hospitalisation due to RSV–associated ALRI in children with DS. Meta–analyses were performed on extracted data using STATA statistical software, and hospitalisation rates for children with and without DS under the age of 2 were calculated.

Findings 5 articles were ultimately deemed eligible for analyses. Analyses were limited to children under the age of 2 years. We calculated the hospitalisation rate for children with DS in this age group to be 117.6 per 1000 child–years (95% CI 67.4–205.2), vs a rate of 15.2 per 1000 child–years (95% CI 8.3–27.6) in unaffected children. This indicates DS contributes to a 6.8 (95% CI 5.5–8.4) fold increase in the relative risk of hospitalisation for RSV–associated ALRI.

Interpretation Though limited by a small number of articles, this review found sufficient evidence to conclude DS was a significant independent risk factor for the development of severe RSV–associated ALRI requiring hospitalisation. Further studies are needed to define the impact of DS in conjunction with other comorbidities on the risk of severe RSV infection. Determining benefits of immunoprophylaxis or future vaccines against RSV in this at–risk population is warranted.

Respiratory syncytial virus (RSV) is one of the leading causes of acute lower respiratory tract infections (ALRIs) in young children (<5 years) globally [1–3].

Almost every child will have been infected with RSV by the age of 2 years, and 40% of these will develop ALRIs. Of these, 0.5–2% of children will require hos-

pitalisation, making RSV–associated ALRIs the leading cause of hospitalisation among infants during winter [1]. Prematurity, chronic lung disease, age <6 months, and congenital heart disease (CHD) are established risk factors for RSV infection [4–6]. Bloemers et al. highlighted Down syndrome (DS) as an independent risk factor for RSV infection [7].

DS is the single most common chromosomal abnormality among live born infants, characterised by congenital and dysmorphic features [8]. Individuals with DS are more prone to numerous health issues, and the condition is associated with an overall increased risk of mortality [9,10]. Notably, ALRIs are the most common cause of hospitalisation among children with DS [11]. However, the burden of RSV–associated ALRI in children with DS is unclear. Further investigation into the epidemiology of RSV infection in paediatric DS populations may help optimise patient care in this vulnerable group.

We aimed to estimate the disease burden of RSV–associated ALRI in children with DS, focussing on hospitalisation and severity of disease. We also aimed to quantify the effect of DS as a dependent and independent risk factor for hospitalisation with RSV–associated ALRI.

METHODS

Search strategy and selection criteria

We conducted a systematic literature review using a combination of search terms, hand searching of online journals, and scanning of reference lists of identified citations. Two authors (JP and MC) searched the following databases – MEDLINE, Embase, Global Health, CINAHL, LILACS, Web of Science, IndMED, WHOLIS, and SIGLE. Both extracted data independently.

We included primary, population–based studies published between 1995 and March 1, 2017 reporting hospitalisation rates of RSV–associated ALRI in populations with DS over at least one (1) RSV season. Articles not available in English, and articles using an unclear or inconsistent case definition were excluded. Studies satisfying these minimum eligibility criteria were included. The full eligibility criteria are summarised in Table 1.

The review was also registered on the PROSPERO database (Record #59594). Full details of the search strategy used may be found on the PROSPERO database, and in Online Supplementary Document.

Definitions

ALRI has been defined as equivalent to clinical pneumonia, which is characterised by acute–onset cough or respiratory distress with age–adjusted tachypnoea. Down syndrome was defined as equivalent to having trisomy 21 based on medical or census records. RSV–associated ALRI was defined as ALRI in a child who is RSV positive (either based on laboratory confirmation or relevant ICD codes in medical records).

To increase the data available for analysis, methodology for confirming RSV infection or coding were not used as eligibility criteria, with the understanding that this could limit the interpretation of the results. We similarly did not distinguish between first or subsequent hospitalisations.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Primary population–based studies reporting incidence data for RSV ALRI requiring hospitalisation
	Articles with a surveillance period of at least 1 year or 1 RSV season
	Articles reporting case fatality ratios of RSV infection
	Articles assessing the OR or RR for children with DS for at least 1 year
	Articles confirming RSV infection by laboratory diagnosis or hospital discharge records of confirmed RSV
	Articles reporting estimates for children separately by immunoprophylaxis status, if included in the study
Exclusion criteria	All non–primary articles, including reviews, presentations
	Articles not available in English
	Articles not investigating RSV infection as a primary outcome
	Articles using a case definition of influenza or influenza–like illness
	Articles using an unclear or inconsistent case definition

RSV – respiratory syncytial virus, ALRI – acute lower respiratory tract infection, OR – odds ratio, RR – relative risk, DS – Down syndrome

Data extraction

Hospitalisation rates for all populations and subgroups from relevant studies were extracted onto a Microsoft Excel 2013 database. Information regarding study characteristics, diagnostic tests used, and population characteristics was recorded. Outcome data and risk factor effect parameters were extracted if present. Relative risk and hospitalisation rate data were calculated using raw input data as well as reported figures in the reviewed studies.

Data analysis

We conducted meta–analyses of the data using STATA version 11.2 (StataCorp LP, College Station TX, USA). Primary outcomes were hospitalisation rates of RSV–associated ALRI in children with DS or without DS, and the impact of DS on hospitalisation rate expressed as relative risk. Pooled estimates with corresponding 95% CIs were reported based on random effects model (DerSimonian–Laird method) since significant heterogeneity was expected across studies [12,13].

Two meta–analyses were performed: one using hospitalisation rate data, and one with relative risk data. Sensitivity analyses by age were planned, but were not performed due to limited data.

RESULTS

The literature search identified 111 records for screening after excluding duplicates. Of these, 50 articles were reviewed fully, and 5 articles were ultimately identified as meeting our strict eligibility criteria [7,14–17]. This is shown in **Figure 1**.

All 5 studies used passive hospital data and 1 used both active and passive methods of data collection. Study populations were under the age of 2 years [7,14,15,17], except one study which included infants up to 36 months [16]. All studies used hospital in–patient or out–patient data, and did not distinguish between first or repeat hospitalisation episodes. All studies were based in high–income countries: 3 studies were from Europe and 2 were from the USA. No studies in Asia, Africa or South America met eligibility criteria. These articles are summarised in **Table 2** [7,14–17].

Data analyses focused on the <2 years old age group, given the paucity of data beyond this group. The implications of this decision are discussed below.

Hospitalisation rate

Four of the 5 studies were included in the meta–analysis of hospitalisation rates for children under the age of 2 years with and without DS. The meta–analysis found the hospitalisation rate of RSV–associated ALRI in children under the age of 2 years with DS was 117.6 (95% CI 67.5–205.2) per 1000 children per year. Comparatively, the hospitalisation rate of RSV–associated ALRI in children under the age of 2 years without DS was 15.2 (95% CI 8.3–27.6) per 1000 children per year, ($P < 0.01$).

The meta–estimate of relative risk of DS for hospitalisation with RSV–associated ALRI (including data from all 5 studies) in this age group was 6.8 (95% CI 5.5–8.4).

These findings are summarised in **Table 3** and **Figure 2**.

Disease severity data

Four of the 5 studies compared disease severity in children with and without DS; however, this was inconsistent. Distinct criteria were used across the studies, including need for respiratory support [16,17], need for mechanical ventilation [16,17], median duration of hospital stay [14,16,17], and mean duration of stay [15].
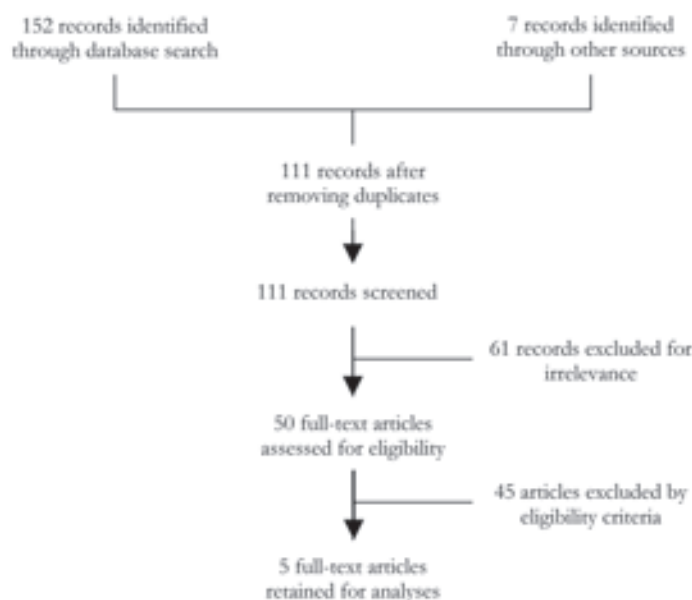
Figure 1. PRISMA flow diagram.

Table 2. Summary of articles in review

Authors	Study setting	Study period	Population	Hospitalisation rate (per 1000 child–years)	OR/RR of hospitalisation (DS vs non–DS)	Severity measurement
Bloemers et al. [7]	Amsterdam and Leiden, Netherlands	1976 – 2005	<36 mo; 395 DS; 276 non–DS; Not receiving palivizumab	DS: 98.7 (72.1–135.1) / Non–DS: 7.3 (1.8–29.0)	13.6 (3.3–56.4)	
Fjaerli et al. [14]	Akershus, Norway	1993 – 2000	<2 y; 7 DS; 70 other non–DS high–risk; 687 non–DS; Low–risk	DS: 153.9 (76.9–307.6) / Non–DS: 14.0 (13.1–15.0)	11.0 (5.5–22.0)	Median LoS; DS: 7.5 d; Non–DS: 4 d; (P<0.001)
Kristensen et al. [15]	Denmark	1997 – 2003	0 – 23 mo;399 DS; 391 584 non–DS	DS: 195.5 (156.6–244.0) / Non–DS: 27.5 (27.0–28.0)	7.1 (5.7–8.9)	Mean LoS; DS: 1.91 d; Non–DS: 1.0 d; (P<0.001)
Stagliano et al. [16]	USA	2005 – 2011	<36 mo; 842 DS; 632 358 non–DS	DS: 96.2 (77.4–119.6) / Non–DS: 14.2 (13.9–14.5)	6.8 (5.5–8.4)	Need for respiratory support; DS: 9.3%; Non–DS: 1.8%; (P<0.001); Median LoS; DS: 4 d; Non–DS: 2 d;(P<0.01)
Zachariah et al. [17]	Colorado, USA	1995 – 2006	0 – 23 mo; 630 DS;	DS: 67.5 (49.9–91.1) / Non–DS: 12.1 (11.9–12.3)	6.0 (5.4–6.7)	Median LoS; DS: 4–5 d; Non–DS: 2–3 d; (P<0.001)

DS – patients with Down syndrome, Non–DS – patients without Down syndrome, RR – relative risk, OR – odds ratio, LoS – length of stay, d – day, mo – month, y – year

Table 3. Summary of articles, with meta–analyses and sensitivity analyses

Author	RSV–associated ALRI hospitalisation rate among patients with DS, per 1000 child–years (95% CI)	RSV–associated ALRI hospitalisation rate among patients without DS, per 1000 child–years (95% CI)	RR (95% CI)
Bloemers et al. [7]	98.7 (72.1–135.1)	7.3 (1.8–29.0)	13.6 (3.3–56.4)
Fjaerli et al. [14]	153.9 (76.9–307.6)	14.0 (13.1–15.0)	11.0 (5.5–22.0)
Kristensen et al. [15]	195.5 (156.6–244.1)	27.5 (27.0–28.0)	7.1 (5.7–8.9)
Stagliano et al. [16]	96.2 (77.4–119.6)	14.2 (13.9–14.5)	6.8 (5.5–8.4)
Zachariah et al. [17]	67.5 (49.9–91.1)	12.1 (11.9–12.3)	6.0 (5.4–6.7)
Meta–analysis of all articles:			
Meta–analysis for all under 2 years*	117.6 (67.4–205.2)	15.2 (8.3–2.6)	6.8 (5.5–8.4)

RSV – respiratory syncytial virus, ALRI – acute lower respiratory tract infection, RR – relative risk, CI – confidence interval

*Sensitivity analysis using data from Bloemers et al. [7], Fjaerli et al. [14], Kristensen et al. [15], and Zachariah et al. [17] only.

The wide range of severity measures precluded formal analyses of the data; however, within the group of hospitalised children, RSV–associated ALRI was consistently more severe in children with DS compared to those without DS [14–17]. This is shown in **Table 2**.

Comorbidities

Three of the 5 studies investigated the role of comorbid risk factors in the epidemiology of RSV–associated ALRI in children with DS. However, there were inconsistencies in the conditions assessed, and the parameters used.

Only two studies formally assessed the impact of comorbid risk factors; however, analyses were limited to comparing populations with DS and any additional risk factors to populations with DS without any risk factors [7,17]. The inconsistencies between the studies precluded formal meta–analyses of the data. Both studies found the presence of additional risk factors generally did not significantly affect the hospitalisation rate, clinical presentation, or management of RSV–associated ALRI in children with DS [7,17]. However, Zachariah et al. noted a significantly higher use of bronchodilators in populations with DS and at least one additional risk factor compared to populations with DS alone [17].

Importantly, all three studies found an increased hospitalisation rate for RSV–associated ALRI in populations with DS without additional risk factors [7,16,17].

DISCUSSION

To our knowledge, this is the first systematic review and meta–analysis to report global estimates for hospitalisation rates attributable to RSV–associated ALRI in children with DS compared to children without

Figure 2. Forest plots of (a) risk ratio of Down syndrome for respiratory syncytial virus (RSV)–associated ALRI requiring hospitalisation in children under the age of 2 years; (b) hospitalisation rate of RSV–associated acute lower respiratory tract infection (ALRI) in children under the age of 2 years with Down syndrome; and (c) hospitalisation rate of RSV–associated ALRI in children under the age of 2 years without Down syndrome.

DS. This is important since RSV remains a leading cause of ALRIs and hospitalisation among children globally [1,2]. We estimated children under the age of 2 years with DS had a 6.8 times (95% CI 5.5–8.4) increased risk of hospitalisation for RSV–associated ALRI compared to children in the same age group without DS. This suggests DS is an important risk factor for RSV–associated ALRI hospitalisation and comparable to other risk factors like CHD (RR 1.5–2.7) [18–21] and bronchopulmonary dysplasia (RR 10.7) [21].

Though meta–analyses were not performed on severity measures, studies assessing infection severity consistently found more severe RSV–associated ALRI in hospitalized children with DS compared to those without DS. Generally, a higher proportion of children with DS required respiratory support and required longer hospitalisation [14–17].

Down syndrome and RSV infection

Several proposed mechanisms explain the increased susceptibility of children with DS to RSV–associated ALRI. These children are more likely to have airway abnormalities such as poor upper airway tone and abnormal lung development. These may contribute towards a tendency to airway compromise and oedema, and thus severe ALRIs [15,22,23]. Children with DS have also been shown to have high rates of CHD and pulmonary hypertension, both of which are risk factors for severe RSV–associated ALRI [8,20]. While these comorbidities are independent risk factors for the development of severe RSV–associated ALRI, the impact of these risk factors in conjunction with DS remains unclear.

Immunological dysfunction may also have a role: DS has been associated with poor thymus development and lower numbers of B and T cells, which may contribute to prolonged infections and poor microbial clearance [24–27].

Lastly, the presence of DS may be associated with a lower threshold for admission, given the complex care needs which may be present in affected infants. This is particularly true in the first year of life, where there is generally poorer nutritional intake [16,28]. However, this does not fully explain the increased risk suffered by children with DS, and disease severity likely also has a role [7].

Comorbidities and Down syndrome

Only three studies reported hospitalisation rate data in populations with DS and other comorbidities, limiting formal analyses on the role of comorbid risk factors alongside DS in the epidemiology of RSV–associated ALRI [7,16,17].

Children with DS often have other risk factors for severe RSV–associated ALRI. Notably, CHD, a significant risk factor for severe RSV–associated ALRI, is comorbid in up to 55% of children with DS [29,30]. However, the reviewed studies consistently showed children with DS alone remained at significantly greater risk of severe RSV–associated ALRI necessitating hospitalisation [7,16,17].

This review suggests there are limited studies exploring the impact of DS in conjunction with other risk factors in the epidemiology of RSV–associated ALRI. Our preliminary findings suggest children with DS and other risk factors are at similar risk of severe RSV–associated ALRI compared to children with DS alone, but further research is necessary [7,16,17].

Palivizumab prophylaxis for children with Down syndrome

Palivizumab is a monoclonal IgG–1 antibody which has been shown to reduce the incidence of RSV hospitalisation, particularly in high–risk groups [31]. However, due to the high costs associated with it, licensing has largely been limited to high–risk populations such as infants with haemodynamically significant CHD (HSCHD) [32].

This systematic review suggests DS alone is associated with a significantly increased risk of hospitalisation due to RSV–associated ALRI. Furthermore, our results suggest that DS alone is associated with more severe RSV infection. While a meta–analysis could not be performed, the consistency of the findings is striking. However, there are other factors to consider when discussing the benefit of immunoprophylaxis in this population.

There are currently no large randomised–control trials investigating the efficacy of immunoprophylaxis for the prevention of RSV–associated ALRI specifically in children with DS. Yi et al. found a lower rate of RSV–related hospitalisation in infants with DS who were treated with palivizumab compared to a retrospective group of untreated controls [33]. A recent observational study by Mikami et al. investigated the efficacy of palivizumab in preventing RSV–associated hospitalisations in immunocompromised populations, including children with DS. However, the study was uncontrolled, and data for children with DS were not explicitly available. Further studies are therefore required to determine the efficacy of palivizumab in patients with DS.

Currently, guidance for palivizumab variably includes a statement on DS. Where this is explicitly mentioned, the guidance further varies, from not routinely recommended to reasonably recommended [33,34]. Many groups cite uncertainty over the burden of disease and the efficacy of palivizumab immunoprophylaxis in this population as challenges limiting the guidance [33–35].

Despite being at increased risk, no studies investigating RSV vaccination or new immunoprophylactic agents to our knowledge have included children with DS in their study populations. Similarly, further information on the topic will be similarly needed to guide RSV prevention in children with DS. Notably, studies on safety and cost–effectiveness in this at–risk population would be helpful in establishing guidance on this issue.

Study limitations

The main limitation in this study was the small number of articles eligible for analysis. This reflects the paucity of research in this area, and demonstrates the need for further investigation into the epidemiology of RSV–associated ALRIs in populations with DS. Notably, several studies pooled populations with and without immunoprophylaxis, and were therefore excluded from the meta–analyses.

Similarly, data were limited regarding the role of comorbidities and other confounding factors such as CHD and immunodeficiency. Only three studies assessed the role of DS in addition to other risk factors. While all three studies found DS to be an independent risk factor for RSV–associated hospitalization, the role of DS in addition to other risk factors in the epidemiology of RSV–associated ALRI is likely complex and currently not clearly understood [7,15].

In particular, the excess risk carried by DS in conjunction with major risk factors remains unknown, and clarification in this area would help define the vulnerability of this at–risk population.

Inconsistencies between the studies reviewed also limited the internal validity of this study. Due to limited data, analyses were restricted to children under the age of 2 years. While RSV–associated ALRI primarily affects younger infants (<2 years), severe infection has also been reported in older children (<5 years) [2,16]. This may be especially true for children with DS: this review found children with DS were older at admission than control populations, though this was statistically insignificant [14,16,17]. However, at least one study has shown children with DS to be significantly older than unaffected children at time of hospitalisation [36].

Similarly, the reporting of comorbidities and disease severity, where available, was variable. Notably, studies assessing the impact of risk factors did so by the general presence or absence of risk factors, limiting comparisons.

The precise definition of RSV–associated ALRI varied between studies, though they were broadly similar. Differences arose primarily in case ascertainment, with some studies relying on laboratory–confirmed RSV status [7,14] and others using hospital discharge coding [15-17]. Due to paucity of studies, we did not

analyse data by method of case ascertainment. Notably, this review is thus subject to the limitations of the studies included, particularly regarding the accuracy of ICD coding.

Reporting overall hospitalisation rates may over–represent more vulnerable individuals, resulting in inaccurate data. This effect may be exaggerated when considering some guidelines advocate admitting children for social or geographic reasons [37,38]. Risk factors for repeated admission may be distinct from risk factors of severe infection, and these nuances may be lost when measuring hospitalisation rates alone.

A greater limitation in the application of this review is the scope of the review, and the socio–geographical bias of the eligible articles. Only five studies were retained for the meta–analyses, and all were based either in Europe or North America. Notably, no articles from low– and middle–income countries (LMICs) fulfilled eligibility criteria, though previous reviews have highlighted the significant disease burden of RSV–associated ALRI in such countries [2,39]. While DS may reasonably be assumed to be a risk factor everywhere, the burden of disease in these populations may vary depending on local public health programmes.

Another limitation of this review was the age of the studies included in the review. Much of the data used in the meta–analyses came from before 2005. As population health and the efficacy of medical interventions have improved in this time, and continue to do so, it is possible the data do not reflect current trends in RSV–associated ALRI hospitalisation and standards of hospital care; this is especially true in high income settings.

Guidelines for palivizumab immunoprophylaxis have also changed during this time, notably for children with HSCHD [33,40]. The treatment of HSCHD has similarly improved in recent years [41]. Theoretically, correcting HSCHD should reduce the risk of developing RSV–associated ALRI, though there are yet limited data to support this hypothesis. These developments could also affect the data in this review.

Future research

The meta–analysis identified a significant need for good data on the impact of RSV–associated ALRI in populations with DS. Notably, further research into the impact of DS on the epidemiology of RSV–associated ALRI in combination with other risk factors would help clarify the burden of disease in this population. Similarly, research investigating the risk carried by populations with DS over time could give insight into the pathophysiology underlying this relationship. This would also help define the risk of children with DS to develop repeat episodes of RSV–associated ALRI.

Importantly, all the studies included in this review came from high–income countries in Europe or the Americas. Data from other geographic regions, particularly in LMICs, would help identify regional variations, and may help establish guidance for RSV prevention globally.

Similarly, to assess better the role of immunoprophylaxis, studies investigating the efficacy and tolerability of palivizumab specifically in infants with DS are needed. Cost–effectiveness analyses in this population may also be helpful, though these analyses may be limited by geographic variation in the costs and benefit of immunoprophylaxis. Furthermore, as palivizumab immunoprophylaxis becomes introduced more widely, the effects of changing policies on the epidemiology of RSV–associated ALRI in this population should be explored.

CONCLUSION

This is the first systematic review investigating the burden of RSV–associated ALRI in children with Down syndrome. Our findings suggest this population is at significantly greater risk of severe RSV–associated ALRI than unaffected populations, and may benefit from being considered for immunoprophylaxis. Unfortunately, the efficacy of palivizumab in this population is still unclear, and warrants further research, including cost–effectiveness analysis. When vaccines or extended half–life antibodies against RSV will become available, their efficacy should be explored in this vulnerable population.

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PAPERS

Knowledge about mother–to–child transmission of HIV, its prevention and associated factors among Ethiopian women

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Background Poor awareness and knowledge of mother–to–child transmission (MTCT),that accounts for over 90% of new HIV infections among children, might contribute to the HIV epidemics. In Ethiopia, 898 400 children are orphaned due to HIV and AIDS and 200 300 were living with HIV in 2013. The main objective of this study was to examine the knowledge of MTCT of HIV, its prevention (PMTCT) and associated factors among Ethiopian women.

Methods We conducted a cross–sectional analysis among 16 515 women from the Ethiopian Demographic Health Survey (EDHS) 2011. Chi–square test, univarate and multivariable logistic regression analysis were used to examine the associations of socio–demographic variables with women's correct knowledge of MTCT and PMTCT, assessed through five specific questions.

Findings The overall correct knowledge of Ethiopian women about MTCT and PMTCT (correct answers to all the five questions) was very low (34.9%). In the multivariable analysis, residing in urban area (adjusted odds ratio (AOR) = 1.56, 95% CI = 1.35–1.79; $P < 0.001$), having higher education (AOR = 3.25, 95% CI = 2.74–3.86; $P < 0.001$), belonging to higher wealth household (AOR = 1.85, 95% CI = 1.57–2.18; $P < 0.001$), currently in union (AOR = 1.25, 95% CI = 1.12–1.39; $P < 0.001$), occupation (AOR = 1.30, 95% CI = 1.17–1.44; $P < 0.001$) and being exposed to mass media (AOR = 1.55, 95% CI = 1.41–1.70; $P < 0.001$) were strongly associated with women's correct knowledge of MTCT and PMTCT.

Conclusion Strategies to improve the knowledge of MTCT and PMTCT in Ethiopia should focus on rural women, emerging regions, the poor, illiterate and unemployed women. Efforts are also needed to involve religious leaders and related organization in the prevention of mother to child transmission of HIV.

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Although a remarkable achievement has been made and new HIV infections among children have declined by 50% since 2010 globally [1], HIV remains the major cause of child morbidity and mortality in low resource countries. Among the estimated 36.7 million people living with HIV worldwide in 2015, 1.8 million were children under 15 years of age, and among the estimated 1.1 million people who died of AIDS–related illnesses in the same year, 110 000 were children under 15 years of age [1].

Sub–Saharan Africa is the most affected region, with an estimated 25.6 million people living with HIV in 2015. Among the estimated 2.1 million (150 000 children under 15 years of age) new HIV infections globally in 2015, about 66% occurred in sub–Saharan Africa [2].

Ethiopia is one of the Sub Saharan African countries that are highly affected by HIV and AIDS. An estimated 793 700 people were living with HIV in 2014, with adult prevalence rate of 1.5% [3]. Women account for the larger proportion of people living with HIV and AIDS, with a prevalence rate of 1.9% [4]. In 2013, 78000 women (15–49 ages) were newly infected with HIV [5]. Ethiopia is also among the 22 countries with the highest number of pregnant women living with HIV [6]. In 2013, the number of HIV positive pregnant women was estimated to be 36 467 and about 9493 babies were infected with HIV [7]. According to the 2014 country progress report on HIV response, 200 300 children are living with HIV and there were 898 400 orphans due to HIV and AIDS in Ethiopia [3].

Mother–to–child transmission (MTCT) is the most common route of pediatric HIV infection. It accounts for over 90% of new HIV infections among children [8]. Without intervention, the risk of MTCT ranges from 20% to 45%, but it can be reduced to less than 2%, in non–breastfeeding populations and to 5% or less in breastfeeding populations with effective interventions during the periods of pregnancy, labor, delivery and breastfeeding [9,10]. One of the major problems in preventing mother to child transmission of HIV is the poor awareness and knowledge of the people about MTCT and PMTCT.

While several studies have examined the knowledge on MTCT and PMTCT among pregnant women attending antenatal care [11–16] only one study was conducted among a nationally representative sample of Ethiopian women, to determine whether HIV status and knowledge of mother to child–transmission (MTCT) of HIV were associated with antenatal care (ANC) use [17].

Almost all previous studies investigating MTCT and PMTCT knowledge and associated factors in Ethiopia were done among pregnant women attending antenatal care, and were mainly conducted at health facilities, possibly overestimating the magnitude of the level of knowledge on MTCT and PMTCT of HIV. Thus, in order to carry out a more comprehensive assessment, we examined the knowledge of mother to child transmission of HIV, its prevention and associated factors among a large national sample of Ethiopian women.

METHODS

Data source

This study was based on secondary data that were collected for the 2011 Ethiopian Demographic Health Survey (EDHS) which was obtained from USAID–DHS program data sets. EDHS 2011 was conducted by the Ethiopian Central Statistical Agency (ECSA), with a technical assistance from Strategic consulting & communications for a digital world/ICF International and it was part of the worldwide MEASURE DHS project which is funded by the United States Agency for International Development (USAID) [4,18].

Data were collected according to a standard protocol of Demographic and Health Survey (DHS) which had three core survey questionnaires; the Household Questionnaire, the Woman's Questionnaire and the Man's Questionnaire. These questionnaires were translated into three major languages of the country— Amharigna, Afan Oromo, and Tigrigna. The questionnaires were pretested in all three languages before the start of field work and respondents were interviewed by the properly trained interviewers. ICF International staff and representatives from other organizations participated in fieldwork monitoring. A quality control team was present in each of 9 regions and 2 city administrations [4].

Sampling methods

The 2011 EDHS sample was selected using a stratified, two–stage cluster design. In the first stage, the sample included 624 enumeration areas (EAs); 187 in urban areas and 437 in rural areas. In the second stage, a complete listing of households was carried out in each enumeration area. A representative sample of 17 817 households was selected and 17 018 were successfully interviewed, yielding a response rate of 98%. From the sampled households, complete interviews were conducted for 16 515 women aged 15–49 (response rate 95%) and 14 110 men aged 15–59 (response rate 89%), using the relevant questionnaires which were adapted from model survey instruments developed for the MEASURE DHS project.

Data management

After the relevant variables for the current study were identified, five questions and some key socio–demographic factors were extracted from the large data set. The specific data sets for women were explored and all 16 515 women respondents in the age range selected were included in our analysis.

Outcome variable

For our analysis, one general question regarding HIV and AIDS (Q1:"Have you ever heard of an illness called HIV and AIDS?") and 4 other questions (Q2: "the virus that causes AIDS can be transmitted to the baby by breastfeeding?", Q3: "the virus that causes AIDS can be transmitted to the baby during pregnancy?", Q.4: "the virus that causes AIDS can be transmitted to the baby during delivery?") and "Q.5: The Risk of MTCT Can be reduced by taking special drugs (antiretroviral) during pregnancy?" were used to identify the level of respondent's knowledge on mother to child transmission and its prevention of HIV, with category 1 for 'yes' and 0 for 'no'. All respondents who responded "no" and "don't know" in the primary data were added in category "0" for the current study, assuming that both were out of awareness. The outcome of interest for this analysis is "women's correct knowledge of MTCT and PMTCT" and defined as "yes" if the respondent correctly answered all five questions and "no" if the respondent answered any incorrect answer.

Independent variables

All the relevant socioeconomic factors were considered as independent variables in the analysis of this study and categorized accordingly as follows. Age (15–19, 20–29, 30–39 & 40–49), residence (urban vs rural), marital status (never in union, currently married & formerly married), educational level (no education, primary, secondary & above secondary), Religion (Christians, Muslim, and others), region (agrarian regions, emerging regions and city administrations, wealth index (poorest, poorer, middle, richer and richest), Exposure to mass media (yes, no) and occupation (not working, agricultural and nonagricultural).

Regions were categorized based on the existing structure. Currently, Ethiopia is Administratively structured into nine regional states—Tigray, Affar, Amhara, Oromiya, Somali, Benishangul–Gumuz, Southern Nations Nationalities and Peoples (SNNP), Gambela, and Harari—and two city administrations, Addis Ababa and Dire Dawa administration councils. Hence, four big regions (Oromiya, Amhara, SNNPR and Tigray) were categorized as agrarian regions. Four hard to reach regions, most of them are pastoralist, (Somali, Afar, Benishangul Gumuz and Gambela) were categorized as emerging regions. The capital Addis Ababa, Dire Dawa city and Harari region were categorized in same group. Harari region was categorized with two city administrations based on household's wealth index and other common similarities as indicated in DHS 2011. The wealth index was categorized based on a standard set of household assets, dwelling characteristics, and ownership of consumer and taken as pre–calculated in the primary data. Watching television, listening radio and reading newspaper at least once a week was considered as being exposed to mass media for the current study.

Statistical analysis

To identify the background characteristics of respondents in all categories, cross tabulation was done independently. We used chi–square test to check the statistical significance of the associations between the socio–economic variables and a correct knowledge of MTCT and PMTCT. All the variables found to be significant ($P < 0.001$) were entered in to a logistic regression analysis to re–check the associations in univariate, calculate the adjusted odds ratio (AOR, 95% confidence interval. CI) and assess the degree of association between women's correct knowledge on MTCT & PMTCT and each independent variable in multivariable analysis, adjusting for covariates. Associations were considered significant, if $P < 0.05$. All statistical analyses were performed using SPSS software version 22.

FINDINGS

Table 1 presents socioeconomic characteristics of the respondents. From the total 16 515 respondents, the majority (67.7%) were from rural area and almost half (48.3%) were from the agrarian regions. Majority of the participants were less than 30 years of age (60.8%), currently married (61.8%) and Christian (61.2%). Half of the participants (50.1%) were illiterate, 48.4% had no formal work and 35% had no access to mass media.

Table 2 shows the proportion of respondents who correctly answered to questions identified to evaluate the level of respondent's knowledge of MTCT and PMTCT. Most of respondents had heard of an illness called HIV and AIDS (96.3%), and 78.1%, 69.3% and 67.1% knew that MTCT could occur through breast feeding, during delivery and during pregnancy respectively. Only 58.9% knew that there are special drugs to avoid HIV transmission to baby. Although a greater proportion of participants answered correctly to individual questions, only 34.9% correctly responded to all five questions.

Table 1. Distribution of socio–demographic characteristics by knowledge of mother–to–child HIV transmission and prevention of mother–to–child HIV transmission among Ethiopian women

VARIABLES	NUMBER (N = 16515)	PERCENTAGE (%)
Age (years):		
15–19	3835	23.2
20–29	6207	37.6
30–39	4058	24.6
40–49	2415	14.6
Residence:		
Urban	5329	32.3
Rural	11 186	67.7
Current marital status:		
Never in union	4413	26.7
Currently married	10 204	61.8
Formerly married	1898	11.5
Educational level:		
No education	8278	50.1
Primary	5858	35.5
Secondary	395	8.4
Higher	984	6
Religion:		
Christians	10 108	61.2
Muslim	6170	37.4
Others	229	1.4
Region:		
Emerging region	4594	27.8
Agrarian region	7984	48.3
City administration and Harari region	3937	23.8
Wealth index:		
Poorest	3711	22.5
Poorer	2402	14.5
Middle	2268	13.7
Richer	2505	15.2
Richest	5629	34.1
Exposure to mass media:		
No	5766	34.9
Yes	10 736	65
Occupation:		
Not working	7992	48.4
Agricultural	3143	19
Non–agricultural	5229	31.7

The results of χ^2 test that used to check the statistical significance of the associations between the socio–economic variables and a correct knowledge of MTCT and PMTCT are shown in **Table 3**. All the variables found to be significant ($P<0.001$) were entered in to a logistic regression analysis to recheck the associations in univariate, calculate the adjusted odds ratio (AOR, 95%CI) and assess the degree of association between women's correct knowledge on MTCT & PMTCT and each independent variable in multivariate analysis, adjusting for covariates.

Table 4 presents the association between socio–economic variables and correct knowledge of respondents on MTCT and PMTCT in univariate and multivariate analyses. As indicated, the correct knowledge of respondents varied by region and type of residence. Higher proportion of respondents from two city administrations & Harari region (52.6%) and urban dwellers (57.2%) had correct knowledge on MTCT and PMTCT as compared to those from emerging regions (25.5%), agrarian regions (30.2%) and rural area (23.3%).

The result of univariate analyses also showed that age, residence, marriage, education, religion, household wealth, exposure to mass media and occupation were significantly associated with women's correct knowledge of MTCT and PMTCT.

The results of the multivariate analysis that examined the degree of the association between each socioeconomic variable and women's correct knowledge of MTCT and PMTCT of HIV, adjusting for covariates, are shown in **Table 4**. Results are presented as adjusted odds ratios, 95% confidence intervals and percentages. Overall, place of residence, education level, being in union, religion, exposure to mass media and occupation remained strongly associated with women's correct knowledge of MTCT and PMTCT of HIV. The association of living in agrarian regions and belonging to Muslim faith with women's knowledge of MTCT and PMTCT did not reach statistical significance. Logistic regression analysis showed that the higher the education and wealth of respondents, the higher knowledge they have on MTCT and PMTCT of HIV. Women who resided in urban areas, married, with formal work, belonging to Christian faith and those exposed to mass media were more likely to have correct knowledge of MTCT and PMTCT.

Table 2. Knowledge of respondents on mother–to–child HIV transmission and prevention of mother-to-child HIV transmission among Ethiopian women

OUTCOME VARIABLES	NUMBER OF RESPONDENTS (N = 16515)	PERCENTAGE (%)
Ever heard of HIV and AIDS	15 904	96.3
HIV transmitted by breast feeding	12 898	78.1
HIV transmitted during delivery	11 445	69.3
HIV transmitted during pregnancy	11 081	67.1
Drugs to avoid transmission of HIV to baby	9727	58.9
Correct answers to all questions	5648	34.2

Table 3. Associations between socio–demographic variables and correct knowledge on mother–to–child HIV transmission and prevention of mother–to–child HIV transmission in chi–square test

Variables	Correct knowledge		Chi–square	P
	N	(%)		
Total	**5647**	**34.2%**	54.908	<0.001
Age (years):				
15–19 (n = 3835)	1407	36.7		
20–29 (n = 6207)	2236	36.1		
30–39 (n = 4058)	1298	32		
40–49 (n = 2415)	706	29.3		
Residence:			18422.225	<0.001
Rural (n = 11 186)	3045	57.2		
Urban (n = 5329)	2602	23.3		
Current marital status:			227.661	<0.001
Never in union (n = 4413)	1888	42.8		
Currently married (n = 10204)	3063	30		
Formerly married (n = 1898)	696	36.7		
Educational level:			1870.955	<0.001
No education (n = 8278)	1726	20.9		
Primary (n = 5858)	2331	39.8		
Secondary (n = 395)	905	65		
Higher (n = 984)	685	69.7		
Religion:			366.629	<0.001
Christians (n = 10 108)	4017	39.8		
Muslim (n = 6170)	1592	25.8		
Other (n = 229)	35	15.3		
Region:			805.196	<0.001
Emerging region (n = 4594)	1168	25.5		
Agrarian region (n = 7984)	2410	30.2		
City administration &Harari region (n = 3937)	2069	52.6		
Wealth index:			1977.662	<0.001
Poorest (n = 3711)	700	18.9		
Poorer (n = 2402)	513	21.4		
Middle (n = 2268)	516	22.8		
Richer (n = 2505)	733	29.3		
Richest (n = 5629)	3185	56.6		
Exposure to mass media:			1013.699	<0.001
No (n = 5766)	1047	18.2		
Yes (n = 10 736)	4598	42.9		
Occupation:			332.806	<0.001
Not working (n = 7992)	2427	30.4		
Agricultural (n = 3143)	867	27.6		
Non–agricultural (n = 5229)	2297	44		

DISCUSSION

This study found out that, though the majority of the participants were aware of MTCT and PMTCT, the level of correct knowledge they had on mother to child transmission of HIV and its prevention was very low (34.9%). This proportion was lower compared to a survey conducted to determine whether HIV status and knowledge of mother to child–transmission (MTCT) of HIV were associated with ANC use in Ethiopia, which indicated an overall prevalence of women's knowledge on MTCT was 59.9% [17]. It is also lower than the rates observed in facility based studies from Nigeria, Tanzania and Uganda (74.5%, 60%, and 50%, respectively) [19–21].

Residing in urban area, having primary education and above, having higher wealth household, and being exposed to mass media were positively associated with women's correct knowledge of MTCT and PMTCT. These results support similar findings from Ethiopia, Botswana, Tanzania & Bangladesh [22–26]. The fact that women who resided in urban areas were 1.56 times more likely to have correct knowledge of MTCT and PMTCT than rural women could be due to better access of urban residents to health infor-

Table 4. Associations between socio–demographic variables and correct knowledge on mother–to–child HIV transmission and prevention of mother–to–child HIV transmission in univariate and multivariate analyses

Variable	Correct knowledge*	Univariate			Multivariate		
	N (%)	OR	95% CI	P	AOR	95% CI	P
Age (Ref = 15–19):							
15–19 (n = 3835)	1407 (36.7)	Ref	–	–	Ref	–	–
20–29 (n = 6207)	2236 (36.1)	0.97	0.89–1.06	0.511	0.94	0.84–1.05	0.286
30–39 (n = 4058)	1298 (32.0)	0.81	0.74–0.89	<0.001	0.98	0.86–1.12	0.8
40–49 (n = 2415)	706 (29.3)	0.71	0.64–0.80	<0.001	1.02	0.88–1.19	0.766
Residence (Ref = Rural):							
Rural (n = 11 186)	2602 (23.3)	Ref	–	–	Ref	–	–
Urban (n = 5329)	3045 (57.2)	4.4	4.11–4.72	<0.001	1.56	1.35–1.79	<0.001
Marital status (Ref = Never in union):							
Never in union (n = 4413)	1888 (42.8)	Ref	–	–	Ref	–	–
Currently married (n = 10204)	3063 (30.0)	0.57	0.53–0.62	<0.001	1.25	1.12–1.39	<0.001
Formerly married (n = 1898)	696 (36.7)	0.77	0.69-0.87	<0.001	1.28	1.11-1.48	0.001
Educational level (Ref = No education):							
No education (n = 8278)	1726 (20.9)	Ref	-	-	Ref	-	-
Primary (n = 5858)	2331 (39.8)	2.51	2.33-2.70	<0.001	1.77	1.62-1.94	<0.001
Secondary (n = 395)	905 (65.0)	7.03	6.22-7.95	<0.001	2.96	2.56-3.42	<0.001
Higher (n = 984)	685 (69.7)	8.72	7.53 10.09	<0.001	3.25	2.74-3.86	<0.001
Religion (Ref = Other):							
Christians (n = 10 108)	4017 (39.8)	3.66	2.55–5.26	<0.001	1.85	1.26–2.71	0.002
Muslim (n = 6170)	1592 (25.8)	1.93	1.34–2.78	<0.001	1.34	0.91–1.97	0.134
Other (n = 229)	35 (15.3)	Ref	–	–	Ref	–	–
Region (Ref = emerging region):							
Emerging region (n = 4594)	1168 (25.5)	Ref	–	–	Ref	–	–
Agrarian region (n = 7984)	2410 (30.2)	1.27	1.17–1.38	<0.001	0.98	0.89–1.08	0.665
City administration &Harari region (n = 3937)	2069 (52.6)	3.25	2.97–3.56	<0.001	1.12	1.00–1.26	0.047
Wealth index (Ref = Poorest):							
Poorest (n = 3711)	700 (18.9)	Ref	–	–	Ref	–	–
Poorer (n = 2402)	513 (21.4)	1.17	1.03–1.33	0.017	0.99	0.87–1.13	0.885
Middle (n = 2268)	516 (22.8)	1.27	1.12–1.44	<0.001	1.01	0.88–1.16	0.855
Richer (n = 2505)	733 (29.3)	1.78	1.58–2.0	<0.001	1.27	1.11–1.44	<0.001
Richest (n = 5629)	3185 (56.6)	5.61	5.09–6.19	<0.001	1.85	1.57–2.18	<0.001
Exposure to mass media (Ref = No):							
No (n = 5766)	1047 (18.2)	Ref	–	–	Ref	–	–
Yes (n = 10736)	4598 (42.9)	3.38	3.13–3.65	<0.001	1.55	1.47–1.70	<0.001
Occupation (Ref = Not working):							
Not working (n = 7992)	2427 (30.4)	Ref	–	–	Ref	–	–
Agricultural (n = 3143)	867 (27.6)	0.87	0.80–0.96	0.003	1.3	1.17–1.44	<0.001
Non–agricultural (n = 5229)	2297 (44.0)	1.79	1.67–1.93	<0.001	1.12	1.03–1.22	0.007

OR – odds ratio, AOR – adjusted odds ratio, CI – confidence interval

*Correct knowledge indicates correct answers to all five questions.

mation and education through electronic and social medias. Although we didn't analyze the distance between residence and health facilities, the accessibility of health facilities in urban area might be another reason as it is the place where health educations are given to women during ANC and related services. Further study is needed to examine the impact of distance between residence and health facilities, and the role of social medias in raising the awareness and knowledge of women on MTCT and PMTCT.

Having primary education and above, having higher level of wealth quintile and being exposed to mass media were strongly associated with women's correct knowledge of MTCT and PMTCT. For example women who had higher education level and women from the richest household were 3.25 and 1.85 times more likely to have correct knowledge of MTCT and PMTCT compared to the illiterate and poorest women, respectively. The potential explanation might be that educated women have more access to different health information and can capture the content easily. The low level of knowledge on MTCT and PMTCT among the poor women might be due to less access to health services and health information related to MTCT and PMTCT.

Women with access to mass media (watching television, listening radio and reading newspaper at least once a week) were 1.55 times more likely to have correct knowledge of MTCT and PMTCT than those with no access. This finding is consistent with the studies from Kenya and Tanzania [25,27]. Addressing the illiterate and poor women in the PMTCT services and reaching them with target oriented MTCT and PMTCT messages through different mass media is needed to achieve elimination of MTCT.

Women's correct knowledge of MTCT and PMTCT was positively associated with occupation. This finding is in agreement with previous studies from Ethiopia and Kenya [16,28]. A possible explanation is that women who have formal work have better access to health information and education at their work places and through different media compared to unemployed women. Marriage was also positively associated with women's correct knowledge of MTCT and PMTCT. The fact that the women currently in union were 1.25 times more likely to have correct knowledge of MTCT and PMTCT compared to the women never in union could indicate that married woman obtain health information at health facilities during their visit for ANC and related services. Moreover, married women may share information about MTCT and PMTCT with their male partners. Conducting further studies on male's knowledge about MTCT and PMTCT and its impact on male involvement in PMTCT programs is valuable in these regards.

The results also show that Christian women had higher levels of knowledge on MTCT and PMTCT. Women who belonged to Christian faith were 1.85 times more likely ($P=0.002$) to have correct knowledge of MTCT and PMTCT. This fact may indicate the active engagement of churches, religious leaders and related organizations in combating HIV/AIDS in general and in promoting PMTCT programs in particular. Previous studies from Nigeria and Uganda also indicated that religious leaders and organizations can play an important role in raising the awareness of the people to combat HIV and AIDS epidemic [29,30].

The finding of current study regarding women from emerging regions being less likely to have correct knowledge of MTCT and PMTCT compared to those reside in city administration and Harari region is consistent with similar studies conducted in city administrations and emerging region of Ethiopia. For instance, the study conducted in Addis Ababa (city administration) shows 89.8% and 76.8% of respondents having knowledge of MTCT and PMTCT respectively [31]. However, the result of a study conducted in Assosa town (emerging region) found out only 57.5% and 17.4% of respondents had knowledge about MTCT and PMTCT of HIV respectively [32]. Poor access and utilization of PMTCT due to limited access of infrastructures like health facilities, schools, roads, distance from the central government and limited access of media coverage in emerging regions could be possible reasons. The findings of this study have implications for policy makers and all concerned bodies enrolling women who live in emerging regions in PMTCT programs. Hence, more efforts and holistic approaches are needed to intensify health education and all PMTCT related services particularly in these regions.

This study has a number of limitations. First, the primary data were collected for 2011 EDHS and therefore it may not reflect adequately the current situation. Second, as this is a cross–sectional study, it is not possible to make causal inferences and determine the temporal nature of the associations. Third, some variables which may have effect on women's knowledge of MTCT and PMTCT; like ANC services, distance to reach health facilities, HIV counseling and testing, misconceptions of HIV and AIDS were not analyzed in the current study.

However, as it was conducted on national sample of Ethiopian Women, the findings would contribute a lot to interventions aimed at increasing women's awareness and knowledge of mother to child transmission of HIV, its prevention and associated factors. The findings of this study have important implications for policy makers and other concerned bodies. It can also serve as a benchmark for those who want to make a further study to identify the knowledge of general population about MTCT and PMTCT in Ethiopia.

CONCLUSION

The overall level of knowledge of Ethiopian women about MTCT and PMTCT was very low. Our study found out that educated women, women who resided in urban area, women of rich household, women who belonged to Christian faith and those who were exposed to mass media were relatively at a better position to have correct knowledge of MTCT and PMTCT. Women who got married or being in union and had formal work were also more likely to have better knowledge of MTCT and PMTCT. Strategies to improve the knowledge of MTCT and PMTCT in Ethiopia should focus on women who live in rural area, emerging regions, the poor, illiterate and unemployed women. Lastly, efforts are needed to involve religious leaders and related organizations in the prevention of mother to child transmission of HIV across the country.

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Immunization practices in low birth weight infants from rural Haryana, India: Findings from secondary data analysis

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Background Low birth weight (LBW) infants constitute a vulnerable subset of infants with impaired immunity in early life. In India, there is scarcity of studies that focus on immunization practices in such infants. This analysis aimed to examine immunization practices in LBW infants with the intention to identify areas requiring intervention.

Methods Data on immunization status of LBW infants enrolled in an individually randomized, double–masked, placebo–controlled trial of neonatal vitamin A supplementation were analysed. Study outcomes were full immunization by one year of age and delayed vaccination with DPT1 and DPT3. Multivariable logistic regression was performed to identify factors associated with the outcome(s).

Findings Out of 10 644 LBW infants enrolled in trial, immunization data were available for 10 517 (98.8%). Less than one–third (29.7%) were fully immunized by one year of age. Lowest wealth quintile (adjusted odds ratio (AOR) 0.39, 95% confidence interval (CI) 0.32–0.47), Muslim religion (AOR 0.41, 95% CI 0.35–0.48) and age of mother <20 years (AOR 0.62, 95% CI 0.52–0.73) were associated with decreased odds of full immunization. Proportion of infants with delayed vaccination for DPT1 and DPT3 were 52% and 81% respectively. Lowest wealth quintiles (AOR 1.51, 95% CI 1.25–1.82), Muslim religion (AOR 1.41, 95% CI 1.21–1.65), mother aged <20 years (AOR 1.31, 95% CI 1.11–1.53) and birth weight <2000 g (AOR 1.20, 95% CI 1.03–1.40) were associated with higher odds of delayed vaccination for DPT–1. Maternal education (≥12 years of schooling) was associated with high odds of full immunization (AOR 2.39, 95% CI 1.97–2.91) and low odds of delayed vaccination for both DPT–1 (AOR 0.59, 95% CI 0.49–0.73) and DPT–3 (AOR 0.57, 95% CI 0.43–0.76).

Conclusion In this population, LBW infants are at a risk of delayed and incomplete immunization and therefore need attention. The risks are even higher in identified subgroups that should specifically be targeted.

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Approximately 15% of infants born in low and middle income countries (LMIC) have a low birth weight (<2500 g) [1]. In India, around 19% of the babies born have a low birth weight [2]. These infants are at a greater risk of morbidity from vaccine–preventable diseases (VPDs) compared to normal birth weight infants (≥2500 g) [3–5]. Immunization is one of the most important and cost–effective public health interventions to reduce both morbidity and mortality associated with infectious diseases [6]. In order to

achieve maximal protection, a child should receive all recommended immunizations within specified intervals.

Low birth weight (LBW) infants have a lower passive immunity prior to vaccination and also their immune defences are functionally impaired in early life [5,7,8]. Further, immune protection attained through transplacental transfer of maternal immunoglobulins declines rapidly in these babies, exposing them to an increased risk of infections [4,9,10]. Vaccination has been shown to have a similar efficacy and safety in LBW infants compared to normal birth weight babies. This makes a strong case for these infants to be immunized fully and in time. [4,11].

Previous studies, largely from high income countries, suggest that LBW infants are less likely to receive vaccines on time and be fully immunized [12–14]. The proposed reasons were high rates of medical complications, leading to prolonged hospitalization; lack of awareness among parents about benefits of vaccination and concerns about possible harm to these infants, perceived to be feeble and delicate [15–18]. In LMICs, studies have mostly examined immunization coverage and their determinants in children above 12 months, irrespective of their birth weight but such studies do not widen our horizon of understanding of immunization practices in LBW infants, that form a vulnerable subset [19,20].

Recently, few studies have been conducted that document immunization practices in LBW infants from rural Ghana [21,22]. However, in India, where high burden of such babies is of concern, lack of systematic studies obscures our understanding of their immunization practices. This information is essential in order to inform public health policy so that special efforts could be undertaken to improve uptake of immunization services in low birth weight infants. With this background, current secondary analysis was planned to document the immunization practices and their determinants in LBW infants, using data from an individually randomized, double–masked, placebo–controlled trial in rural Haryana, India [23,24]. As a secondary objective, we examined the association of birth weight with immunization practices.

MATERIALS AND METHODS

Study design and setting

The present analysis utilizes data on the immunization status of low birth weight infants enrolled in a large individually randomized, double–masked, placebo–controlled trial of neonatal vitamin A supplementation within 72 hours of birth. This study was conducted in Faridabad and Palwal districts in the state of Haryana, North India from June 2010 to July 2012 [23]. The trial procedures and details of study area have been described previously [23,24].

Ethical clearance

The trial was approved by the ethics review committees of the Society for Applied Studies, World Health Organization (WHO) and by the state government of Haryana. It is registered with ClinicalTrials.gov, number NCT01138449. Permission was taken from all the concerned investigators of the primary trial for this secondary data analysis

Enrolment and data collection

Study teams identified pregnant women through household surveillance at intervals of 3 months in areas allocated to them. The pregnancies identified were followed up until delivery and birth outcomes were reported to the co–ordinators who then informed the enrolment workers immediately [24]. For each live birth identified, the study team visited the family, explained the trial, screened the infant against a pre–defined eligibility criteria (infants aged ≤3 days at screening, could suck or feed and family intended to stay in the study area for at least 6 months) and obtained written consent from at least one parent ie, mother/ father of eligible infants. The enrolled infant was weighed by the study team members who were trained and standardized.

At enrolment, information was collected primarily on household characteristics (social class, religion, wealth quintile), infant characteristics (birth weight, sex, place of delivery, personnel conducting delivery, multiple births), maternal characteristics (number of living children, age, education, occupation) and father's education. Each enrolled infant was allocated a home visit worker for further follow up until 12 months of age. All infants were contacted when aged 29 days and at 3, 6 and 12 months and at each such visit, information was collected on vital status and immunization.

At each visit, the study team member looked for written documentation of vaccines administered to the infant. The documents reviewed were maternal and child health card, immunization card of the infant or any slip(s) issued by the facility where vaccination was done. The study team made several attempts to obtain written documented evidence of vaccination. This included a wait time, to ensure the mother ample time to search for the missing record, telephoning the father for any relevant information, and also postponing the visit to a later date. If the immunization card was still not available the team helped mother to report accurate dates by referring to important events or festivals. Also, the mother was asked to recall which vaccines were given, at what body site and the mode of vaccination (oral or injection). An infant was categorised as "not vaccinated" when the mother reported infant had never been vaccinated.

Outcomes of the secondary analysis

The primary outcomes were full immunization by one year of age and delayed vaccination with DPT1 and DPT3 in LBW infants. In concordance with the guidelines of the National Immunization Program in India, an infant was considered "fully immunized" if he/she had received BCG, 3 doses of DPT, OPV each and measles by one year of age [25]. Hepatitis–B immunization was not considered as a part of full immunization as the vaccine was not introduced during the time of trial in the state of Haryana [26]. There is no standard approach to the assessment of delayed vaccination and several definitions have been described [27,28]. However, previous studies have considered DPT–1 and DPT–3 vaccination as acceptable points to assess delay [13,21].

Operationally, "delayed vaccination" was defined as having received the vaccine after 4 weeks of recommended/due time [21,29,30]. In India BCG is to be given at birth; OPV–1 and DPT–1 at 6 weeks of age; OPV–2 and DPT–2 at 10 weeks of age, OPV–3 and DPT–3 at 14 weeks of age; measles at 9 months of age [25]. For the primary analysis, a delay in DPT–1 was considered when the LBW infant was vaccinated later than 10 weeks of age and for DPT–3, when the infant was vaccinated at >18 weeks of age.

Additionally, sensitivity analysis was done to assess whether delayed DPT3 vaccination reflected delayed DPT1 vaccination. Starting with follow–up at receipt of DPT1 vaccination, an infant was labelled as having a "delayed receipt" of DPT–3 when it was given >12 weeks after DPT–1 (according to National Immunization Schedule, the time interval between DPT–1 and DPT–3 should be 8 weeks).

Data analysis

For the analyses, infants with known vaccination status, dates of vaccination and with complete data on covariates were included. Infants who were lost to follow–up or died before the vaccination due date, were excluded. This principle was followed for all the time points of analysis. Data analysis was performed using STATA version 11 (Stata Corporation, College Station, TX). Proportions were calculated for all categorical variables used in the analysis. Median (interquartile range; IQR) was calculated for delay in vaccination (in days), from the recommended time, for each of the vaccine that was considered in the analysis. Chi–square test was done to compare proportions and Wilcoxon–Mann–Whitney 2– sample rank sum test to compare medians across the two birth weight categories.

Multivariable logistic regression was performed to identify factors associated with full immunization and delayed vaccination. Bivariate analysis was first done for all explanatory variables and those with a P–value of <0.20 were then included in the final multivariable logistic regression model [31,32]. A P–value of <0.05 was considered statistically significant in the final regression model. Explanatory variables considered were household characteristics (wealth index, religion. social class); maternal and paternal characteristics (maternal age, maternal education, maternal occupation, paternal education); birth related characteristics (place of delivery, personnel conducting delivery, multiple births, and number of living children) and infant characteristics (birth weight and sex).

Additionally, to assess the association of birth weight on study outcome(s) ie, "full immunization "and "delayed vaccination", regression analysis was done with birth weight as the exposure variable (in dichotomous form ie, ≥2500 and <2500 g) and adjustment done for other covariates. Assessment for effect modification (ie, potential interaction) between birth weight and all covariates was done using interaction term in the model. Likelihood ratio test was used to compare models with or without the interaction term. Sensitivity analysis was also conducted where data collected only from immunization cards were analysed to document the determinants of full immunization and delayed vaccination in low birth weight infants. Analysis to document the determinants of full immunization and delayed vaccination in normal birth weight infants was also undertaken on an exploratory basis.

RESULTS

Characteristics of the infants recruited in the primary trial

A total of 44 984 infants were recruited in the primary trial, within 72 hours of birth, out of which 10 644 (23.7%) were low birth weight infants. This subset of LBW infants was analysed for the primary outcome(s). However, to give a general sense of how these low birth weight infants compared to their normal birth weight counterparts, a comparative description of the characteristics have been presented (**Table 1**). The proportion of female infants was more in the LBW category (55.5%) compared to normal birth weight (NBW) infants (45.6%) (**Table 1**). The mean (SD) birth weight of normal and low birth weight infants was 2914.0 (421.0) and 2193.1 (224.3) grams respectively. A similar proportion of LBW and NBW infants were born at home (44.6% vs 42.8%). Most of the LBW infants had mothers with low literacy (50.3% of mothers reported having no education or not completing primary school) and 11% had mothers with age less than 20 years (**Table 1**). In NBW infants, low maternal literacy was observed in 44.4% and around 7% (2388/34,340) had mothers aged less than 20 years.

Figure 1 shows the flow of infants recruited in the primary trial, starting from the time of recruitment ie, within 2 days of birth, until the age of 1 year. Out of the 10 644 LBW infants that were enrolled, 847 died by the end of one year (infant mortality rate of 79.6/1000 live births). A large proportion of the deaths occurred in the first 6 weeks of life (n = 404/847; 47.4%). In normal birth weight infants, there were a total of 971 deaths in the first year of life, resulting in an infant mortality rate of 28.3/1000 live births.

Immunization practices among the low birth weight infants

Out of the total 10 644 LBW infants that were enrolled in the trial, immunization data was available for 10 517 (98.8%). In 77.8% infants, data was obtained through "immunization card" and in rest; it was elicited through reliable history. Low birth weight infants had a comparatively lower immunization uptake compared to normal weight infants, both in terms of the proportion that received a particular vaccine and also in appropriateness of timing of receiving vaccine (**Table 2**). Around three–fourth received BCG vaccine (75.9%) and one–fifth (20.3%) received zero–dose of polio vaccine. The proportion that received DPT–1, DPT–2, DPT–3 and measles vaccine was 74.1%, 58.3%, 45.4% and 35.6% respectively. Less than one–third (29.7%) were fully immunized by one year of age ie, had received BCG, three doses of DPT and OPV each and measles vaccine.

There was a delay in the time of receipt of the vaccines compared to the recommended time as per the National Immunization Schedule. The median (interquartile range; IQR) delay for BCG, DPT–1, DPT–2 and DPT–3 was 41 (19–75), 30 (12–63), 46 (23–89) and 62 (34–112) days respectively. Around 65% of the LBW babies had delay in receiving BCG, 52% in DPT–1, 68% in DPT–2 and 81% in DPT–3. For measles vaccine, the median (IQR) delay from the recommended time was 24 (9–46) days and around two–fifth infants (43.5%) had delay in receiving the vaccine.

Determinants of full immunization in LBW babies

Out of 9779 LBW infants that were alive at the age of 1 year, 2913 (29.7%) were fully immunized. There was a dose response relationship between wealth quintiles and full immunization status.
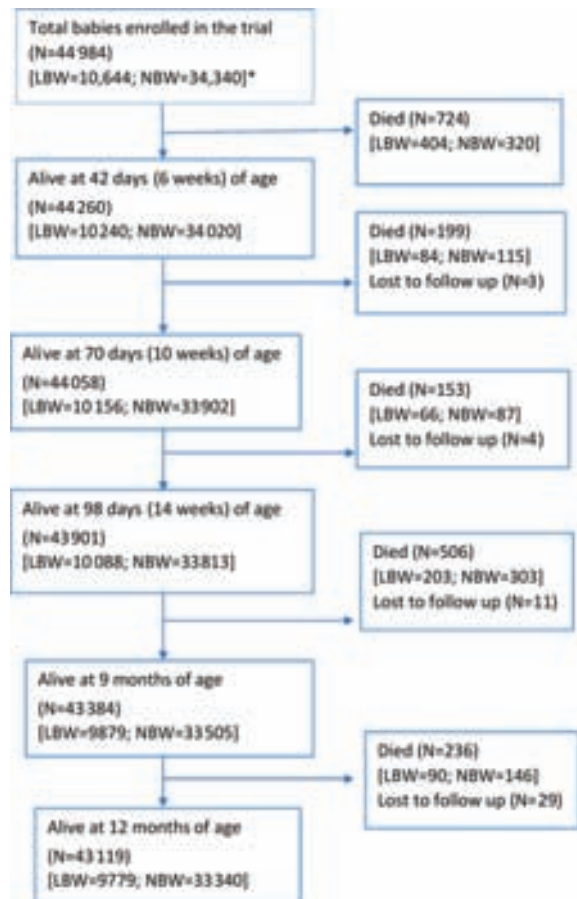
Figure 1. Flow of infants recruited in the primary trial. *LBW – low birth weight; NBW – normal birth weight. The flow shows the number of alive babies at 6, 10, 14 weeks and at 9 and 12 months of age specifically with the intention of present the number of babies eligible for OPV1/DPT1 (given at 6 weeks), OPV2/DPT2 (given at 10 weeks), OPV3/DPT3 (given at 14 weeks) and Measles (given at 9 months of age).

Table 1. Baseline characteristics of the primary trial population, segregated by low and normal birth weight infants (N = 44 984)

Variables	Normal birth weight (≥2500 g; n = 34 340)	Low birth weight (<2500 g; n = 10 644)
Household characteristics		
Quintiles:*		
1 (Least poor)	7391 (21.5)	1613 (15.1)
2	7043 (20.5)	1947 (18.3)
3	6873 (20.0)	2124 (20.0)
4	6628 (19.3)	2369 (22.3)
5 (Poorest)	6405 (18.7)	2591 (24.3)
Religion:*		
Hindu	26 401 (76.9)	8171 (76.8)
Muslim	7582 (22.1)	2323 (21.8)
Others	357 (1.0)	148 (1.4)
Social class:*†		
General	9587 (27.9)	2453 (23.1)
Other Backward Class (OBC)	16 583 (48.3)	5308 (49.8)
Scheduled Caste/Tribe (SC/ST)	8170 (23.8)	2881 (27.1)
Maternal and paternal characteristics		
Mother's age (in years):*		
<20	2388 (6.9)	1175 (11.0)
20–25	22 705 (66.1)	7097 (66.7)
26–30	7159 (20.9)	1784 (16.8)
>30	2088 (6.1)	588 (5.5)
Mother's education (years of schooling):*		
Illiterate (0)	13 895 (40.5)	4918 (46.2)
Less than primary (1 to <5)	1351 (3.9)	433 (4.1)
Primary completed and secondary incomplete (5 to <12)	14 847 (43.2)	4418 (41.5)
Secondary complete and higher education (≥12)	4247 (12.4)	875 (8.2)
Mother's occupation:		
Employed outside home	888 (2.6)	252 (2.4)
Home maker	33 452 (97.4)	10 392 (97.6)
Father's education (years of schooling):*		
Illiterate (0)	4367 (12.7)	1652 (15.5)
Less than primary (1 to <5)	1617 (4.7)	600 (5.7)
Primary completed and secondary incomplete (5 to <12)	19 396 (56.5)	6336 (59.5)
Secondary complete and higher education (≥12)	8960 (26.1)	2056 (19.3)
Birth related characteristics		
Place of delivery:*		
Home	14 694 (42.8)	4753 (44.6)
Government facility	10 863 (31.6)	3273 (30.8)
Private facility	8783 (25.6)	2618 (24.6)
Personnel conducting delivery:*		
Skilled	21 187 (61.7)	6371 (59.9)
Unskilled	13 153 (38.3)	4273 (40.1)
No. newborns:*		
Singleton	34 245 (99.7)	10 168 (95.5)
Multiple	95 (0.3)	476 (4.5)
No. of living children (apart from the infant enrolled):*‡		
0	10 501 (30.6)	4226 (39.7)
1–2	17 489 (50.9)	4938 (46.4)
3–4	3293 (9.6)	761 (7.1)
≥4	3057 (8.9)	719 (6.8)
Infant characteristics		
Sex of the baby:*		
Male	18 676 (54.4)	4742 (44.5)
Female	15 664 (45.6)	5902 (55.5)

*Statistically significant difference in proportion across the two groups (P<0.05); Others – Christian/Sikh/Jain/Parsi/Zoroastrian/Buddhist/neo Buddhist.

†General – group that do not qualify for any of the positive discrimination schemes by Government of India (GOI); OBC – term used by the Government of India to classify castes which are socially and educationally disadvantaged; SC/ST – official designations given to groups of historically disadvantaged indigenous people in India [33].

‡Excluding the baby recently born/enrolled in the study.

Table 2. Immunization uptake among normal birth weight (≥2500 g) and low birth weight (<2500 g) babies in rural Haryana, North India

Vaccines under National Immunization Schedule	Number*			Proportion received (%)			Deviation from recommended time (days) of vaccination, median (IQR)†			Proportion with delay (%)		
	LBW	NBW	Overall	LBW	NBW	Overall	LBW	NBW	Overall	LBW	NBW	Overall
BCG	10 517	34 262	44 779	75.9‡	80.8	79.6	41 (19–75)‡	39 (18–70)	39 (18–71)	64.4‡	62.7	63.1
OPV–0†				20.3‡	22.2	21.8	–	–	–	–	–	–
OPV–1	10 240	34 020	44 260	64.4‡	68.9	67.9	27 (10–56)‡	24 (9–52)	25 (10–53)	48.1‡	44.6	45.4
DPT–1				74.1‡	78.3	77.3	30 (12–63)‡	27 (11–58)	27 (11–59)	51.7‡	47.9	48.7
OPV–2	10 156	33 902	44 058	51.5‡	57.5	56.1	44 (21–84)‡	41 (20–77)	42 (20–79)	65.7‡	63.6	64.0
DPT–2				58.3‡	63.9	62.7	46 (23–89)‡	44 (21–82)	44 (21–84)	67.8‡	65.5	65.9
OPV–3	10 088	33 813	43 901	40.8‡	46.6	45.3	60 (33–107)‡	59 (31–101)	59 (32–102)	79.6‡	77.8	78.2
DPT–3				45.4‡	51.2	49.9	62 (34–112)‡	60 (32–104)	61 (32–105)	80.7‡	78.7	79.1
Measles (at 9 months)	9879	33 505	43 384	35.6‡	41.2	39.9	24 (9–46)‡	22 (8–43)	22 (8–44)	43.4‡	41.1	41.6
Fully immunized at 1 year of age	9779	33 340	43 119	29.7‡	35.2	34.0	–	–	–	–	–	

LBW – low birth weight, NBW – normal birth weight

*For 205 babies (all died in the first month of life) information on immunization was not available, 724 babies died at or before 42 days (6 weeks) of age, 923 died at or before 70 days (10 weeks) of age, 1076 died at or before 98 days (14 weeks) of age, 1582 died at or before 270 days (9 months) of age, 1818 died within one year.

†According to the National Immunization Schedule (Government of India). BCG and OPV-0 at birth, OPV-1/DPT-1 at 6 weeks of age, OPV-2/DPT-2 at 10 weeks of age, OPV-3/DPT-3 at 14 weeks of age and Measles at 9 months of age.

‡Statistically significant difference (P<0.05) compared to normal birth weight babies.

§Data not available on the time of receiving of birth dose of polio vaccine.

Those LBW infants who were from the lowest wealth quintile had the lowest odds compared to those in highest wealth quintile (adjusted odds ratio (AOR) 0.39; 95% confidence interval (CI), 0.32–0.47] (**Table 3**). Belonging to a Muslim family (AOR 0.41; 95% CI, 0.35–0.48), mother's age <20 years (AOR 0.62; 95% CI, 0.52–0.73) delivered by unskilled attendant (AOR 0.77; 95% CI, 0.64–0.91) and being a female (AOR 0.84; 95% CI, 0.77–0.92) decreased the odds. With increasing number of living children a women had, the odds of fully immunizing the recently delivered LBW baby decreased; the lowest odds in those with ≥4 children (AOR 0.58; 95% CI, 0.43–0.77) (**Table 3**).

Compared to infants with illiterate parents, those with mothers [AOR 2.39; 95% CI, 1.97–2.91] and fathers [AOR 1.49; 95% CI 1.22–1.83] who were educated until secondary school or higher (≥12 years of schooling) had increased odds of full immunization. Mother's age was also an important determinant. Compared to mother's aged 20–25 years, those aged 26–30 years [AOR 1.38; 95% CI, 1.19–1.58] and >30 years [AOR 1.49; 95% CI, 1.15–1.95] had higher odds of getting their child fully immunized. Also, delivery at a government health facility [AOR 1.29; 95% CI, 1.08–1.54] increased the odds (**Table 3**).

In the sensitivity analysis, using data documented through immunization cards, 15.2% of LBW infants were fully immunized by 12 months of age. The determinants of full immunization in these infants were essentially similar to those obtained when combined data obtained through immunization cards and reliable histories were analysed (Table S1 in **Online Supplementary Document**). Lower wealth quintile, belonging to a Muslim family, mother's age <20 years, delivered by unskilled attendant, ≥4 living children for the woman and female sex of the infant were associated with decreased odds. Unlike in the combined analysis wherein father's education was associated with increased odds of the child for being full immunized, in the sensitivity analysis, father's education did not emerge as a statistically significant determinant. However, mother's education and delivery at the government health facility were associated with increased odds.

Determinants of delayed vaccination in LBW babies

Lowest wealth quintiles [AOR 1.51; 95% CI, 1.25–1.82], Muslim religion (AOR 1.41; 95% CI, 1.21–1.65), mother aged <20 years (AOR 1.31; 95% CI, 1.11–1.53) and birth weight <2000 g (AOR 1.20; 95% CI, 1.03–1.40) were associated with higher odds of delayed vaccination with first–dose of DPT (DPT–1) vaccine (**Table 4**). On the other hand, higher maternal education (AOR 0.59; 95% CI, 0.49–0.73) and

Table 3. Determinants of full immunization at one year of age among low birth weight babies in rural Haryana, North India

Variables	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)*	P-value
Household characteristics				
Quintiles:				
1 (Least poor)	Ref.		Ref.	
2	0.70 (0.61–0.81)	<0.001	0.83 (0.71–0.95)	0.010
3	0.45 (0.38–0.51)	<0.001	0.61 (0.52–0.71)	<0.001
4	0.35 (0.30–0.40)	<0.001	0.54 (0.46–0.64)	<0.001
5 (Poorest)	0.19 (0.16–0.22)	<0.001	0.39 (0.32–0.47)	<0.001
Religion:				
Hindu	Ref.		Ref.	
Muslim	0.24 (0.21–0.28)	<0.001	0.41 (0.35–0.48)	<0.001
Others†	0.96 (0.67–1.37)	0.824	1.23 (0.84–1.79)	0.284
Social class:				
General	Ref.		Ref.	
Other Backward Class	0.52 (0.46–0.57)	<0.001	1.10 (0.97–1.24)	0.122
Scheduled Caste/Tribe	0.75 (0.67–0.84)	<0.001	1.30 (1.14–1.49)	<0.001
Maternal and paternal characteristics				
Mother's age (in years):				
<20	0.59 (0.51–0.69)	<0.001	0.62 (0.52–0.73)	<0.001
20–25	Ref.		Ref.	
26–30	0.94 (0.83–1.06)	0.305	1.38 (1.19–1.58)	<0.001
>30	0.62 (0.49–0.77)	<0.001	1.49 (1.15–1.95)	0.003
Mother's education (years of schooling):				
Illiterate (0)	Ref.		Ref.	
Less than primary (1 to <5)	1.48 (1.16–1.88)	0.001	1.23 (0.96–1.58)	0.105
Primary completed and secondary incomplete (5 to <12)	2.61 (2.36–2.89)	<0.001	1.56 (1.39–1.75)	<0.001
Secondary complete and higher education (≥12)	5.56 (4.76–6.50)	<0.001	2.39 (1.97–2.91)	<0.001
Father's education (years of schooling):				
Illiterate (0)	Ref.		Ref.	0.203
Less than primary (1 to <5)	1.27 (0.97–1.66)	0.075	1.19 (0.91–1.58)	<0.001
Primary completed and secondary incomplete (5 to <12)	2.53 (2.17–2.95)	<0.001	1.53 (1.29–1.81)	<0.001
Secondary complete and higher education (≥12)	4.51 (3.80–5.35)	<0.001	1.49 (1.22–1.83)	
Birth related characteristics				
Place of delivery:				
Home	Ref.		Ref.	
Government facility	1.97 (1.78–2.19)	<0.001	1.29 (1.08–1.54)	0.004
Private facility	1.98 (1.77–2.22)	<0.001	0.96 (0.79–1.15)	0.649
Personnel conducting delivery:‡				
Skilled	Ref.		Ref.	
Unskilled	0.45 (0.41–0.48)	<0.001	0.77 (0.64–0.91)	0.003
No. of living children:				
0	Ref.		Ref.	
1–2	0.86 (0.78–0.95)	0.002	0.89 (0.79–0.98)	0.031
3–4	0.56 (0.46–0.68)	<0.001	0.70 (0.56–0.88)	0.002
>4	0.32 (0.26–0.41)	<0.001	0.58 (0.43–0.77)	<0.001
No. newborns:				
Singleton	Ref.		Ref.	
Multiple	1.29 (1.04–1.61)	0.019	1.14 (0.89–1.45)	0.302
Infant characteristics				
Birth weight (in grams):				
2000–2499	Ref.		Ref.	
<2000	0.88 (0.76–1.03)	0.104	0.88 (0.75–1.03)	0.122
Sex of the baby:				
Male	Ref.		Ref.	
Female	0.86 (0.78–0.93)	<0.001	0.84 (0.77–0.92)†	<0.001

OR – odds ratio, Ref. – reference value
*Variables with P-value <0.20 in the bivariate analysis were included in the multivariable analysis and have been presented in the table. Mother's occupation had a P-value of ≥0.20 in bivariate analysis and was not included in the multivariable analysis
† Others – Christian/Sikh/Jain/Parsi/Zoroastrian/Buddhist/neo Buddhist.
‡Skilled attendant included doctor/nurse/Auxiliary Nurse Midwife/community health worker; unskilled included traditional birth attendant/relative/neighbour.

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Table 4. Determinants of delayed vaccination with first dose DPT at age >10 weeks and third dose DPT at age >18 weeks for low birth weight babies in rural Haryana, North India

Variables	DPT–1 (at >10 weeks after birth)				DPT–3 (at >18 weeks after birth)			
	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)*	P-value	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)*	P-value
Household characteristics								
Quintiles:								
1 (Least poor)	Ref.		Ref.		Ref.		Ref.	
2	1.36 (1.18–1.57)	<0.001	1.26 (1.09–1.47)†	0.002	1.19 (0.96–1.47)	0.110	1.04 (0.83–1.30)	0.742
3	1.49 (1.29–1.72)	<0.001	1.32 (1.13–1.55)†	0.001	1.04 (0.83–1.29)	0.736	0.84 (0.65–1.07)	0.150
4	1.48 (1.28–1.71)	<0.001	1.27 (1.08–1.51)†	0.005	1.07 (0.86–1.34)	0.537	0.83 (0.64–1.08)	0.164
5 (Poorest)	1.93 (1.66–2.24)	<0.001	1.51 (1.25–1.82)†	<0.001	1.20 (0.93–1.55)	0.157	0.83 (0.61–1.14)	0.266
Religion:								
Hindu	Ref.		Ref.		Ref.		Ref.	
Muslim	1.66 (1.44–1.90)	<0.001	1.41 (1.21–1.65)†	<0.001	1.31 (0.99–1.73)	0.055	1.06 (0.79–1.43)	0.680
Others‡	1.17 (0.81–1.70)	0.404	1.12 (0.77–1.64)	0.554	1.78 (0.88–3.59)	0.106	1.59 (0.79–3.24)	0.194
Social class:								
General	Ref.		Ref.		Ref.		Ref.	
Other Backward Class	1.28 (1.15–1.43)	<0.001	1.00 (0.89–1.13)	0.990	1.28 (1.07–1.53)	0.006	1.17 (0.96–1.41)	0.113
Scheduled Caste/Tribe	1.18 (1.04–1.33)	0.008	0.97 (0.85–1.11)	0.704	0.97 (0.81–1.17)	0.783	0.89 (0.72–1.08)	0.243
Maternal and paternal characteristics								
Mother's age (in years):								
<20	1.40 (1.21–1.63)	<0.001	1.31 (1.11–1.53)†	0.001	1.36 (1.04–1.81)	0.027	1.31 (0.97–1.73)	0.060
20–25	Ref.		Ref.		Ref.		Ref.	
26–30	1.05 (0.92–1.19)	0.475	0.95 (0.83–1.09)	0.467	0.98 (0.81–1.21)	0.906	0.97 (0.79–1.19)	0.792
>30	1.22 (0.97–1.52)	0.080	0.92 (0.71–1.19)	0.521	1.08 (0.72–1.61)	0.706	0.97 (0.64–1.45)	0.871
Mother's education (years of schooling):								
Illiterate (0)	Ref.		Ref.		Ref.		Ref.	
Less than primary (1 to <5)	0.82 (0.64–1.05)	0.116	0.87 (0.68–1.11)	0.274	0.76 (0.51–1.13)	0.177	0.77 (0.51–1.15)	0.212
Primary completed and secondary incomplete (5 to <12)	0.76 (0.68–0.84)	<0.001	0.86 (0.77–0.97)†	0.014	0.88 (0.74–1.05)	0.162	0.86 (0.71–1.05)	0.131
Secondary complete and higher education ≥12	0.47 (0.39–0.55)	<0.001	0.59 (0.49–0.73)†	<0.001	0.58 (0.46–0.72)	<0.001	0.57 (0.43–0.76)†	<0.001
Father's education (years of schooling):								
Illiterate (0)	Ref.		Ref.		Ref.		Ref.	
Less than primary (1 to <5)	1.02 (0.79–1.32)	0.857	1.06 (0.82–1.37)	0.648	0.86 (0.54–1.38)	0.547	0.91 (0.56–1.47)	0.703
Primary completed and secondary incomplete (5 to <12)	0.84 (0.73–0.97)	0.018	1.02(0.87–1.19)	0.831	0.87 (0.66–1.15)	0.328	0.93 (0.69–1.25)	0.634
Secondary complete and higher education (≥12)	0.67 (0.67–0.78)	<0.001	1.07 (0.88–1.29)	0.502	0.72 (0.53–0.95)	0.025	0.87(0.62–1.21)	0.406
Birth related characteristics								
Place of delivery:								
Home	Ref.		Ref.		Ref.		Ref.	
Government facility	0.68 (0.61–0.75)	<0.001	0.81 (0.68–0.96)†	0.017	0.72 (0.60–0.86)	<0.001	0.79 (0.60–1.06)	0.126
Private facility	0.82 (0.73–0.92)	0.001	1.08 (0.91–1.29)	0.377	0.79 (0.66–0.95)	0.014	0.88 (0.66–1.18)	0.409
Personnel conducting delivery:§								
Skilled	Ref.		Ref.		Ref.		Ref.	
Unskilled	1.41 (1.28–1.55)	<0.001	1.15 (0.96–1.37)	0.114	1.32 (1.11–1.56)	0.001	1.08 (0.81–1.45)	0.589

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Table 4. Continued

Variables	DPT–1 (at >10 weeks after birth)				DPT–3 (at >18 weeks after birth)			
	Unadjusted OR (95% CI)	P–value	Adjusted OR (95% CI)*	P–value	Unadjusted OR (95% CI)	P–value	Adjusted OR (95% CI)*	P–value
No. of living children:								
0	Ref.		Ref.		Ref.		–	–
1–2	0.95 (0.86–1.05)	0.312	0.93 (0.84–1.04)	0.204	0.97 (0.84–1.13)	0.725		
3–4	1.28 (1.05–1.56)	0.013	1.14 (0.92–1.43)	0.235	1.24 (0.86–1.77)	0.247		
>4	1.37 (1.09–1.72)	0.006	1.09 (0.83–1.43)	0.544	1.18 (0.75–1.85)	0.473		
No. newborns:								
Singleton	Ref		–	–	Ref		–	–
Multiple	0.98 (0.78–1.23)	0.878			0.99 (0.69–1.42)	0.977		
Infant characteristics								
Birth weight (in grams):								
2000–2499	Ref.		Ref.		Ref.		Ref.	
<2000	1.23 (1.06–1.43)	0.007	1.20 (1.03–1.40)†	0.019	1.06 (0.83–1.37)	0.602	1.04 (0.81–1.34)	0.774
Sex of the baby:								
Male	Ref.		–	–	Ref.		–	–
Female	0.95 (0.87–1.05)	0.340			0.92 (0.79–1.07)	0.275		

*Variables with P-value <0.20 in the bivariate analysis were included in the multivariable analysis and have been presented in the table, exception being the birth weight which was placed in the multivariable regression model irrespective of the p-values in bivariate analysis as this was considered an essential variable determining delay. Mother's occupation had a P-value of ≥0.20 in bivariate analysis and was not included in the multivariable analysis.

†Statistically significant at P<0.05.

‡Christian/Sikh/Jain/Parsi/Zoroastrian/Buddhist/neo Buddhist.

§Skilled attendant included doctor/nurse/Auxiliary Nurse Midwife/community health worker; unskilled included traditional birth attendant/relative/neighbour.

delivery in a government facility (AOR 0.81; 95% CI, 0.68–0.96) were associated with lower odds of delay for DPT–1. Interestingly, maternal education status was the only variable that was significantly associated with delay in receiving third dose of DPT (DPT–3). Infants of mothers with ≥12 years of schooling (ie, secondary school complete and higher education) had lower odds of delay (AOR 0.57; 95% CI, 0.43–0.76) for DPT–3 compared to those with illiterate mothers (**Table 4**).

In the sensitivity analysis, using data obtained through immunization cards, 46.6% and 79.2% of the LBW infants had delay in vaccination for DPT–1 and DPT–3 respectively. Lower wealth quintiles, Muslim religion, mother aged <20 years and birth weight <2000 g were associated with higher odds of delayed vaccination with first–dose of DPT (DPT–1) vaccine (Table S2 in **Online Supplementary Document**). On the other hand, higher maternal education (AOR 0.56; 95% CI, 0.45–0.71) and delivery in a government facility (AOR 0.71; 95% CI, 0.57–0.86) were associated with lower odds of delay for DPT–1. For DPT–3, higher maternal education was associated with reduced odds of delayed vaccination (AOR 0.56; 95% CI, 0.41–0.76).

Birth weight as a determinant of full immunization and delayed vaccination

Low birth weight was associated with reduced odds of full immunization (AOR 0.85; 95% CI, 0.81–0.90) (**Table 5**). For both DPT–1 and DPT–3, a statistically significant interaction was obtained between birth weight and sex (P–value for interaction = 0.0006 and 0.020 respectively). Low birth weight was associated with increased odds of delayed vaccination for DPT–1 (AOR 1.18; 95% CI, 1.10–1.28) and DPT–3 (AOR 1.18; 95% CI, 1.04–1.33) in male infants but there was no such significant association in female infants. After adjusting for the late vaccination with DPT–1, birth weight had no significant association with delay in DPT–3 vaccine (**Table 5**).

Additional findings

As part of the exploratory analysis, determinants of full immunization and delayed vaccination were also documented for normal birth weight infants. Lower wealth quintiles, belonging to Muslim community, mother's age <20 years and female sex were associated with low odds to full immunization, largely similar to

Table 5. Birth weight as a determinant of full immunization and delayed vaccination in infants from rural Haryana, North India

VARIABLES	PROPORTION (%)	UNADJUSTED OR (95% CI)	P–VALUE	ADJUSTED OR (95% CI)*	P–VALUE
Full immunization	**Fully immunized (n) / Alive at 1 year (No.); (%)**				
Birth weight (grams):					
≥2500	11760/33340; (35.2)	Ref.		Ref.	
<2500	2913/9779; (29.7)	0.78 (0.74–0.82)	<0.001	0.85 (0.81–0.90)	<0.001
Delayed vaccination	**No. with delayed vaccination (n) / total No. that received the vaccine (N); (%)**				
DPT–1 (at >10 weeks) by sex of the infant (P–value for interaction = 0.0006)					
Male infants – Birth weight (grams):					
≥2500	6835/14737; (46.3)	Ref.		Ref.	
<2500	1800/3443; (52.3)	1.27 (1.17–1.36)	<0.001	1.18 (1.10–1.28)	<0.001
Female infants – Birth weight (grams):					
≥2500	5918/11892; (49.7)	Ref.		Ref.	
<2500	2123/4148; (51.2)	1.05 (0.98–1.14)	0.116	1.02 (0.94–1.09)	0.592
DPT–3 (at >18 weeks) by sex of the infant (P–value for interaction = 0.020)					
Male infants – Birth weight (grams):					
≥2500	7639/9818; (77.8)	Ref.		Ref.	
<2500	1737 /2135; (81.3)	1.24 (1.11–1.40)	<0.001	1.18 (1.04–1.33)	0.008
Female infants – Birth weight (grams):					
≥2500	5986/7513; (79.6)	Ref.		Ref.	
<2500	1962/2450; (80.1)	1.03 (0.92–1.15)	0.664	0.99 (0.88–1.12)	0.984
DPT–3 after 12 weeks of DPT–1†					
Birth weight (grams):					
≥2500	9207/17315; (53.1)	Ref.		Ref.	
<2500	2506/4579; (54.7)	1.06 (0.99–1.14)	0.061	1.04 (0.97–1.12)	0.183

*Adjusted for infant sex, multiple births, place of delivery, personnel conducting delivery (skilled/unskilled), mother's education, mother's age, mother's occupation, father's education, religion, social class, wealth quintiles and number of living children the women had.
†Adjusted for delayed vaccination for DPT–1.

that observed in low birth weight infant. Higher maternal education and delivery at a government facility were associated with increased odds of full immunization and decreased odds of delayed vaccination. They are presented in Table S3 and S4 in **Online Supplementary Document**.

DISCUSSION

The present secondary data analysis aimed to understand immunization practices in low birth weight babies and elucidate their determinants. Only a third of LBW infants were fully immunized and majority had delayed vaccination for DPT–1 and DPT–3. The findings pertain to study districts where overall immunization performance is lower compared to other districts of the state. These study districts are recognized as "low performing" by the government of Haryana, based on the indicators for uptake of immunization services [34,35]. However, even though these are "difficult" districts in terms of immunization coverage, this situation is what it would be in many parts of India. The determinants of delay and incomplete immunization that have been identified in this study are over and above the health system's issues.

The strength of this study is the robust population– based surveillance system and low loss to follow up. All babies were recruited within 72 hours of birth and weight measured by trained study team, thereby reducing chances of misclassification of infants by birth weight. To achieve adequate quality of data on vaccination status, the study team members were rigorously trained and underwent periodic inter and intra observer standardization exercises [23].

A limitation that must be considered while interpreting the findings is that the main trial excluded sick babies or those that were unable to feed. Such babies would include a certain proportion of LBW infants (possibly the smallest/with lowest birth weight) and in them, the delay and incompleteness in vaccination may be possibly of greater magnitude. Excluding them, therefore, may underestimate the actual delay and incompleteness in immunization. Also, in this setting, we recognize that a small proportion of pregnant women, especially those having the first baby, tend to go to their parents home for delivery and these were therefore not available for enrolment. The immunization practices of these primigravida moth-

ers could be different from those who would have had children previously and this might have possibly affected the findings observed. There was no reliable data on gestational age and so through the current analysis, it would be difficult to interpret whether the immunization practices were influenced by prematurity or not. In around one–fifth of the infants, data on immunization was obtained through reliable history instead of documented evidence in form of immunization card. Thus, the possibility of reporting inaccurate vaccination dates cannot be ruled out. Other factors that could affect immunization uptake such as maternal illness and distance from the health facility were not considered as data was unavailable for these variables. Delayed immunization and low rates of full immunization could also be due to factors affecting supply ie, shortage of vaccines and skilled manpower and other logistic issues but these have not been considered in the current analysis.

After adjustment for potential confounders, being born with low birth weight emerged as a significant determinant of full immunization, and in male infants, also for delayed vaccination with DPT–1 and DPT–3. Interestingly, it was not associated with delay for either DPT–1 or DPT–3 vaccination in females. It could possibly mean that family members/caregivers might hesitate vaccinating their LBW infant, early in life, as they are considered fragile and this fear may be more for male babies, as they are valued more in a patriarchal society like that of Haryana. Lower wealth quintiles, Muslim religion and young maternal age (<20 years) were found to be associated with lower odds of full immunization and higher odds of delayed vaccination for DPT–1 in the final multivariable model. This is in concordance with findings from earlier studies [21,36–38]. Belonging to a lower wealth quintile might represent limited financial ability to access quality health care services whereas young maternal age may suggest mother's lack of knowledge and preparedness towards adequate care of the infant [39]. Previous studies have documented minority religions such as Muslims as a subset of population that are resistant to uptake of immunization services, as they consider it to be detrimental to the infant's health [36,37].
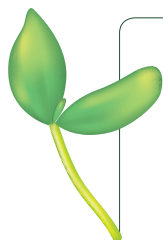
In the final regression model; female sex of the infant, delivery by an unskilled attendant and increasing number of children a woman had were also associated with low odds of full immunization. Social constructs in traditional Indian society subject females towards unequal treatment, notably in the state of Haryana. Studies have reported a household level gender– based differential in terms of allocation of food, care seeking and education, usually with the female child being neglected [40–42]. Delivery by an unskilled attendant might be considered as initial cue towards inadequate health care seeking behaviour of the family. The opportunity for an initial exposure to desired and recommended child care practices through a skilled birth attendant is usually lost when delivery is conducted by unskilled personnel. With increasing number of siblings, the infant was less likely to be fully immunized. This could be attributed to the possible increase in responsibilities for the mother, leading to limited attention to the infant. Previous studies have cited "mothers being busy" as an important reason for inadequate immunization practices for their children [20,43].

Similar to previous studies, in this study as well, high maternal education was found to be strongly associated with improved vaccination status of the infant [44,45]. Increasing access to education for girls and young women is clearly a priority. It will produce multiple benefits for health and development, as well as support sustained improvement in infant and child care practices. From a short term perspective, even targeted health literacy interventions in mothers, irrespective of their education status, could improve child care practices including appropriate uptake of immunization services. Increased maternal age (mainly 30 years and older) had higher odds of full immunization. This might be due to experience accrued by the mother with time on benefits of immunization. Delivery at a government health facility was associated not only with increased odds of full immunization but also with lower odds of delayed vaccination. This finding is interesting and reassuring at the same time. Availability of vaccines free of cost in a government facility might have led to improved immunization practices.

CONCLUSIONS

To the best of our knowledge, it is one of the few data presented from LMIC, particularly in India, to understand the immunization practices in LBW infants and their determinants. The findings show that immunization uptake in these infants was inadequate. Strengthening of essential newborn care practices early in life, with a focus on timely initiation of vaccination and ensuring full immunization should form the linchpin of the low birth weight infant care package. In the current study, poor immunization uptake was observed in the economically weaker sections of the society. This calls for due emphasis on ensuring equity in terms of utilization of immunization services and improving coverage.

Data surveillance and monitoring should routinely focus on identifying groups that are underserved by vaccination. Mobilization activities need to focus on infants from the marginalized sections of the society. Interventions aimed at delaying the age at child birth, addressing female bias, providing targeted education on the importance of immunization to mothers of child bearing age and to women of certain religious communities could prove beneficial. Promoting institutional births and emphasizing on immunization as an integral part of the discharge counselling package would be warranted. Interventions that target the determinants should necessarily be accompanied by efforts to improve the health system.

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PAPERS

Developmental and behavioural problems in children with severe acute malnutrition in Malawi: A cross–sectional study

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Background Early childhood development provides an important foundation for the development of human capital. Although there is a clear relation between stunting and child development outcomes, less information is available about the developmental and behavioural outcomes of children with severe acute malnutrition (SAM). Particularly an important research gap exists in Sub–Saharan Africa where there is a high prevalence of SAM and a high rate of co–occurring HIV (human immune deficiency virus) infection. Our first objective was to assess the prevalence and severity of developmental and behavioural disorders on a cohort of children admitted to an inpatient nutritional rehabilitation centre in Malawi. Our second objective was to compare the developmental and behavioural profiles of children with the two main phenotypes of SAM: kwashiorkor and marasmus.

Methods This was a cross–sectional observational study including all children hospitalized with complicated SAM in Blantyre, Malawi over an 8–month period from February to October 2015. At discharge, children were assessed with the well-validated Malawi Developmental Assessment Tool (MDAT) for gross motor, fine motor, language and social development. In children ≥24 months, emotional and behavioural problems were measured using the Strengths and Difficulties Questionnaire (SDQ).

Results 150 children (55% boys) with SAM were recruited; mean age of 27.2 months (standard deviation 17.9), 27 children (18%) had pre–existing neurodisabilities (ND) and 34 (23%) had a co–occurring human immune deficiency virus (HIV) infection. All children with SAM experienced profound delays in the gross and fine motor, language and social domains. Linear regression analysis demonstrated that children with kwashiorkor scored 0.75 standard deviations lower (95% confidence interval −1.43 to −0.07) on language MDAT domain than children with marasmus when adjusted for covariates. The prosocial behaviour score of the SDQ was low in children with SAM, indicating a lack of sensitive behaviour in social interactions.

Conclusions Children with SAM have severe developmental delays after a hospital admission. Our results indicate that there might be a significant difference in developmental attainment between children with kwashiorkor and with marasmus. Future studies exploring longer–term outcomes and testing possible intervention strategies are urgently needed.

Early childhood development provides an important foundation for the development of human capital. For the first time, child development is included in the new Sustainable Development Goals (SDGs) [1]. In the recent series on child development in *The Lancet*, it is now estimated that children in Sub-Saharan Africa are the most "at-risk" for not reaching their developmental potential (66% in 2010) [2]. The first "1000 days" of life (conception to age 2) are particularly crucial for both nutrition and child development [3]. During this time, rapid growth, including brain development, places high demands on nutrition [3].

Previous literature has described the complex interactions between malnutrition, developmental delay and neurodisability, although clinically it is not always easy to explain a cause–effect relationship [4-8]. Furthermore, it is known that children with neurodisability (eg, cerebral palsy) have a higher risk of malnutrition [4,9]. Conversely, it is also clear that malnutrition is an important risk factor for poor child development [5,10]. In particular, there are strong associations identified between stunting (chronic malnutrition, defined by low height–for–age) and motor and cognitive development in children two years of age or younger [5,6,11,12]. Less attention has been paid to behavioural outcomes in malnourished children [13]. Scarce evidence suggests some differences in behaviour, eg, more negative affect, reduced activity, play and exploration between children who are stunted and those who are not [14].

In contrast to the amount of evidence on stunted children, developmental and behavioural outcomes in children with severe acute malnutrition (SAM) have hardly been studied. With SAM affecting some 19 million children worldwide, this is an important evidence gap [11]. The event of an acute extreme calorie shortage in children with SAM could have different implications on a child's developmental outcome other than the chronic shortage of calories that occurs in children who are stunted [15]. Grantham–McGregor's seminal papers did describe poor levels of development (cognitive and educational) in children post–SAM in Jamaica at the age of 2 years and further work followed up 17 of these children to 14 years [16-18]. These studies were conducted pre–HIV (human immune deficiency virus) and used different case definitions and treatment strategies for SAM thus limiting the applicability to todays' SAM–affected populations. Only one other study has investigated developmental outcomes of children with SAM as part of an intervention study in Bangladesh. HIV status was not mentioned in this study and it is unclear how the Bayley's Scales of Infant and Child Development (2nd version) had been adapted and validated for use in Bangladesh [19]. To our knowledge, no studies have investigated the developmental and behavioural outcomes of SAM in Sub–Saharan Africa where there is a high rate of co–occurring HIV infection in children with SAM [15,20]. "Play therapy" is one of WHO's "10 steps" in the treatment of in-patient SAM but it is unclear how many nutritional rehabilitation centres are actually managing to implement this [21]. In order to inform policy makers and justify future developmental interventions in this population, further evidence is needed on not just the developmental but also the behavioural outcomes of SAM in this setting [22]. The primary aim of this study was to assess developmental and behavioural problems in children with SAM at time of hospital discharge in Malawi. Our first objective was to assess the prevalence and severity of developmental and behavioural disorders on a cohort of children admitted to an inpatient nutritional rehabilitation centre in Malawi. Our second objective was to compare the developmental and behavioural profiles of children with the two main phenotypes of SAM: kwashiorkor and marasmus.

METHODS

Study design and setting

This was a cross–sectional observational study, covering all children hospitalized for treatment of SAM in the nutrition ward of Queen Elizabeth Central Hospital (QECH), in Blantyre, Malawi, over an 8–month period from February to October 2015. QECH is a tertiary referral hospital but mainly serves as a district hospital. Children with SAM either self–present or are referred by local health category with "complicated" SAM: they have medical problems requiring inpatient care (eg, Integrated Management of Childhood Illness danger signs; pneumonia, diarrhoea); or have failed an "appetite test" (defined as the inability to eat Ready to Use Therapeutic Food) [23]. The height, weight and mid–upper–arm circumference (MUAC) of children were measured using standard WHO–based protocols and assessed using WHO 2006 child growth standards [24].

Children were defined with marasmus when they presented with MUAC<11.5cm for children less than 5 years old, or a weight–for–height z–score<–3 on the WHO growth standard [24]. Children were defined with kwashiorkor if they presented with bilateral nutritional oedema [24].

Our study included children who were participating in the "F75 trial" [ClinicalTrials.gov Identifier: NCT02246296], a randomized controlled trial of a reduced carbohydrate formulation of F75 therapeutic milk vs the traditional "F75" therapeutic milk, among children aged 6 months to 8 years with SAM. Both types of milk were only used for a short duration during the stabilisation phase and therefore would likely have no effect on the developmental outcomes. Our sample size was determined by the inclusion of children in the main study. We undertook developmental and behavioural assessments on discharge from the unit when children were clinically stable, finishing all food and had a good appetite as assessed by the clinician. Children were excluded if their parents refused to give informed consent.

Measures

A trained and experienced research assistant (KC) with 2 years of experience with the Malawi Developmental Assessment Tool (MDAT), as well as training on the WHO UNICEF Care for Child Development Package, administered the measures of both child development and behaviour in a quiet room next to the malnutrition unit. The caregiver was present during the complete assessment. During the study period, the development assessments were independently observed by two of the authors, both paediatricians (MH, WV). In addition, after 3 months KC participated in a refresher course of the development assessment tool.

The Malawi Development Assessment Tool (MDAT)

The MDAT is a culturally relevant developmental assessment tool that has been created for the use in African settings [25]. It examines development in the domain of gross motor, fine motor and language development through direct observation of the child as well as social development through questions to the caregiver. Cognitive items are embedded in the fine motor and language domains of the MDAT. It has 136 items (34 in each domain of development). Items are scored as "pass" or "fail" and if the child is uncooperative as "don't know". The MDAT has demonstrated good construct validity and sensitivity in predicting moderate to severe developmental delay in children from birth to 6 years of age and has normative values for a population of children which reflect the demographic and health surveys of the population [25]. The MDAT has good reliability in the healthy Malawian children (standardized Cronbach's alpha 0.98 for all domains [26]) and in our SAM population without neurodisabilities (n = 121), reliability was good for the fine motor and language domain (standardized Cronbach's alpha 0.84 and 0.81 respectively) and acceptable for the gross motor and social domain (standardized Cronbach's alpha: 0.76 and 0.77 respectively).

The MDAT has also demonstrated good sensitivity in detecting more subtle developmental problems in children with marasmus [25]. We calculated MDAT z–sores with the use of the MDAT reference population scores [25]. A domain z–score < –1.64 is suspect for developmental delay; this z–score identifies children who are performing worse than 68.26% of the normed population.

During the MDAT assessment, child and maternal behaviour was observed by the research assistant and reported in an observation form. This form had been adapted from the Behavior Observation Inventory from the Bayley Scales of Infant and Toddler Development [27]. It consisted of 5 items reporting about the child's affect, engagement, anxiety and cooperativeness and about the caregiver's involvement during the assessments. These five questions were chosen based on a previous study rating children's behavior during development assessments in anemic children in a low–income country [28]. Since our research assistant was the only one using this observation tool, it was not translated.

Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a brief 25 item behavioural screening instrument. It is subdivided into four difficulty scales; emotional symptoms, conduct problems, inattention–hyperactivity, peer problems, and a separate fifth strength scale that enquires about the child's behaviour in normal social interactions the "prosocial behaviour" scale [29,30]. All subscales had five questions each. An impact supplement inquires further about the existence, chronicity, and distress of problems, social and learning impairment, and burden to others [14]. Each item has to be scored on a 3–point scale with 0 = "not true", 1 = "somewhat true" and 2 = "certainly true". An example of a question in the inattention–hyperactivity subscale is: "Restless, overactive, cannot stay still for long". The SDQ Total Difficulties Score (TDS) can be calculated by aggregating the scores for each difficulty scale, a higher SDQ–TDS indicates more emotional and behavioural problems. The SDQ has been used worldwide, including low– and middle–income African countries [31,32]. The SDQ has been translated into Chichewa (Malawian language), however no standardized reference

values are available in Malawi (or any other African country) [33,34]. The SDQ has been validated in children older than 2 years [35]. The research assistant therefore only administered the SDQ to caregivers of children 2 years and older in our study. The internal reliability of the SDQ–TDS in our study was 0.73 (standardized Cronbach's alpha) in children with SAM without severe neurodisabilities (n = 51), which is considered to be acceptable.

Covariates

Neurodisability (ND) and HIV infection are common problems underlying SAM in our setting and are associated with poorer outcomes [4,15]. Children with ND will, by definition, have developmental delays in some areas and are more likely to have emotional and behavioural problems [36,37]. In our study, children were considered as having a ND if the caregiver provided a history of severe developmental delay and/or cerebral palsy at admission or this history was described in the child's health passport.

Children with HIV have a higher risk of developmental and behavioural problems [38,39]. All children admitted with SAM were offered an HIV antibody rapid test (Abbott Laboratories, USA) as standard of care. If this first rapid test was positive, a "Uni–Gold" test (Trinity Biotech PLC, Ireland) was performed. If both tests were positive, children were considered to have an HIV infection. Baseline data about the use of co–trimoxazole prophylaxis and/or antiretroviral therapy was collected.

The following other clinically important covariates were also collected: age, sex, child disease characteristics reported during the hospital admission (severe pneumonia, diarrhoea, malaria) and family characteristics (details on the primary and secondary caregiver and parental education level).

Analysis

We used descriptive statistics to evaluate the child's background characteristics and the child and caregiver's involvement in the development assessment. χ^2 tests were used to analyse differences in child health and family characteristics between the marasmus and kwashiorkor group.

For the MDAT domains, z–scores, means and standard deviations were calculated for the entire SAM group and separately for marasmus and kwashiorkor patients. The proportion of children that had a delay in a MDAT domain (ie, had a domain score < –1.64) was computed for all groups. In addition, we examined the association between the type of SAM (marasmus or kwashiorkor) and MDAT domain z–scores with linear regression analysis. Second, we performed a linear regression analysis adjusted for clinically important covariates: gender, HIV, no education or some primary education of the primary caregiver and passive mother involvement during MDAT assessment. All children with pre–existing ND and children older than 6 years were excluded from the MDAT analysis.

Finally, we evaluated the SDQ scores in children with only SAM (SAM Only), in children with SAM and a concurrent HIV infection (SAM + HIV) and children with SAM and a pre–existing ND (SAM +ND). We used analyses of variance (ANOVA) to test for differences between these groups. All data was analysed with IBM SPSS version 20 software (www.ibm.com, New York, NY, USA).

RESULTS

Our study period was 3 months shorter than the F75 trial. In this period a total of 249 children were included, 46 (18.5%) died and 189 were discharged to community care; 39 (20.6%) children were lost to follow–up at discharge. Reasons for loss to follow–up at discharge included that some parents wanted to leave the hospital before the developmental assessment could be done and the unavailability of our research assistant. **Figure 1** shows the flowchart for
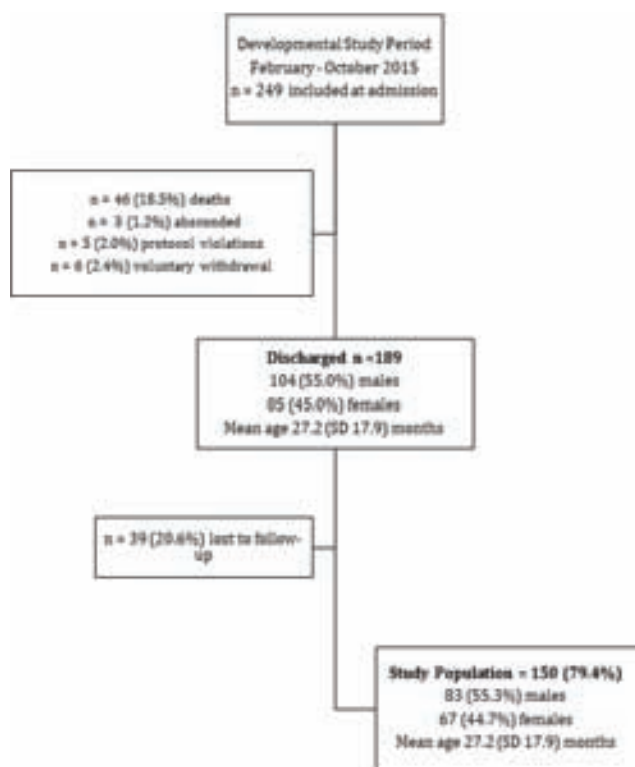
Figure 1. Flowchart for data collection. SD – standard deviation.

Table 1. Background characteristics of the sample by nutritional status

CHARACTERISTICS	MARASMUS	KWASHIORKOR
Number of children	65 (43.3)	85 (56.7)
Boys (n, %)	31 (47.7)	49 (57.6)
Age, months (SD)	21.8 (17.2)	31.3 (17.5)
Admission, days (SD)	5.7 (3.0)	6.8 (3.6)
Anthropometric measurements:		
Weight (kg, SD)	6.3 (2.0)	9.0 (2.5)
Length (cm, SD)	71.5 (10.8)	79.1 (7.9)
MUAC (cm, SD)	10.6 (1.2)	12.4 (1.6)
Weight–for–length z–score (SD)	–3.7 (1.0)	–1.8 (1.8)
Length–for–age z–score (SD)	–3.7 (1.7)	–3.3 (1.6)
Weight-for-age z-score (SD)	-4.6 (1.1)	-3.0 (1.6)
Health characteristics:		
Pre-existing neurodisability (n, %)*	17 (26.2)	10 (11.8)
HIV (n, %)†	23 (35.4)	11 (12.9)
Co-trimoxazole prophylaxis (n, %)	15 (23.1)	8 (9.4)
Highly active antiretroviral therapy (n, %)	5 (7.7)	7 (8.2)
Severe pneumonia	6 (9.2)	7 (8.2)
Diarrhea	22 (33.8)	32 (37.6)
Malaria	8 (12.3)	13 (15.3)
Family characteristics:		
Primary caregiver (n, %):		
Mother	61 (93.8)	77 (90.6)
Grandparent	2 (3.1)	6 (7.1)
Other	2 (3.1)	2 (2.4)
Highest education level (n, %):		
No education	3 (4.6)	7 (8.2)
Some primary education	51 (78.5)	62 (72.9)
Completed primary education	3 (4.6)	1 (1.2)
Some secondary education	7 (10.8)	14 (16.5)
Completed secondary education	1 (1.5)	1 (1.0)
Secondary caregiver (n, %):		
Father	44 (67.7)	53 (62.4)
Grandparent	10 (15.4)	14 (16.5)
Other	8 (12.3)	13 (14.3)
No secondary caregiver	3 (4.6)	5 (5.9)
Highest education level (n, %):		
No education	13 (20.0)	10 (11.8)
Some primary education	20 (30.8)	39 (45.9)
Completed primary education	10 (15.4)	2 (2.4)
Some secondary education	16 (24.6)	16 (18.8)
Completed secondary education	10 (15.4)	13 (15.3)

SD – standard deviation
*χ^2 analysis $P = 0.023$.
†χ^2 analysis $P = 0.001$.

data collection. Our final study population included 150 (79.4%) children discharged after an admission with SAM to outpatient–based care with a mean age of 27.2 months (standard deviation (SD) 17.9). In our study population, 83 (55.3%) were boys, 27 (18%) had pre–existing ND and 34 (22.7%) had a concurrent HIV infection.

Characteristics of the marasmus and kwashiorkor groups

Table 1 shows the background characteristics according to nutritional diagnosis. Children with marasmus had a significant higher percentage of HIV (35.4% vs 12.9%, $P = 0.001$) and pre–existing ND (26.2% vs 11.8%, $P = 0.023$) compared to those with kwashiorkor (**Table 1**). There were no other statistically significant differences in child health and family characteristics between the two groups.

Developmental outcomes

All children with SAM experienced profound delays in the gross and fine motor, language and social domains (**Table 2**). Only the language domain mean z–score in children with marasmus had a score above the cut–off score for a delay (<–1.64). Of all children with SAM, 80% had a delay in the gross motor domain, this included 41 (85%) of the children with marasmus, and 57 (78%) of the children with kwashiorkor (**Table 2**). 32 (44%) children with kwashiorkor compared with 16 (33%) of the children with marasmus were identified with a delay in all 4 MDAT domains ($P = 0.250$).

Linear regression analysis demonstrated that children with kwashiorkor had a significantly lower language MDAT z–score than children with marasmus (–0.75; 95% confidence interval (CI) –1.43 to –0.07), adjusted for covariates (**Table 3**). Additionally, in the unadjusted linear regression analysis children with kwashiorkor had a significantly ($P = 0.024$) lower social MDAT z–score than children with marasmus, but this effect became non–significant when we adjusted for covariates ($P = 0.056$). The other MDAT domain z–scores did not differ with statistical significance between children with marasmus and kwashiorkor (**Table 3**).

Approximately a quarter of the children with SAM were not engaged: and 19% of those with kwashiorkor and 25% of those with marasmus were described as "mostly sad" during the developmental assessments. In 31% and 27% of kwashiorkor and marasmus cases respectively, mothers were described as "passively watching" and not engaged in the child's play. There were no significant differences in the child's affect ($P = 0.210$) engagement ($P = 0.670$), anxiety ($P = 0.600$) and cooperativeness ($P = 0.740$) of the child and in the caregiver's involvement ($P = 0.370$) between the marasmus and kwashiorkor groups (**Table 4**).

Behavioural outcomes

The mean (SD) SDQ–TDS scores were 10.1 (4.2), 12.2 (5.5) and 15.5 (3.8) in the children with SAM Only, SAM+HIV and SAM + ND respectively. **Table 5** describes the SDQ Total Difficulties scores and the scores on the different subscales of the SDQ. The children with SAM+ND had a significantly higher SDQ–

Table 2. MDAT z–scores and percentage suspect for delay by nutritional status*

Status	SAM (n = 121)		Marasmus (n = 48)		Kwashiorkor (n = 73)	
	Mean (SD)	Delay (n, %)	Mean (SD)	Delay (n, %)	Mean (SD)	Delay (n, %)
Gross Motor	–3.1 (1.9)	98 (79.7)	–3.0 (1.8)	41 (85.4)	–3.1 (1.8)	57 (78.1)
Fine Motor	–2.9 (1.2)	90 (73.2)	–2.8 (1.7)	37 (77.1)	–2.9 (2.6)	53 (72.6)
Language	–1.6 (1.7)	59 (48.0)	–1.2 (1.5)	20 (41.7)	–1.9 (1.8)	39 (53.4)
Social	–2.8 (2.4)	85 (69.1)	–2.2 (1.5)	31 (64.6)	–3.2 (2.8)	54 (74.0)

MDAT – Malawi Development Assessment Tool, SAM – severe acute malnutrition, SD – standard deviation
*Children with pre–existing ND (n = 27) and children older than 6 years (n = 2) were excluded from this analysis.

Table 3. Associations between nutritional status and developmental z–scores on MDAT domains: results of linear regression analyses comparing children with kwashiorkor with those with marasmus*

MDAT domain	Unadjusted B (95% CI)	P–value	Adjusted† B (95% CI)	P–value
Gross Motor	–0.07 (–0.78 to 0.65)	0.85	–0.16 (–0.94 to – 0.61)	0.68
Fine Motor	–0.22 (–1.05 to 0.61)	0.61	–0.24 (–1.14 to – 0.65)	0.59
Language	–0.76 (–1.39 to –0.14)	0.018	–0.75 (–1.43 to – 0.07)	0.032
Social	–0.99 (–1.86 to –0.13)	0.024	–0.91 (–1.84 to – 0.02)	0.056

MDAT – Malawi Development Assessment Tool CI – confidence interval
*Children with pre–existing ND (n = 27) and children older than 6 years (n = 2) were excluded from this analysis
†Adjusted for gender, HIV, no education or some primary education of the primary caregiver and passive mother involvement during MDAT assessment. B–coefficients are estimates for difference in MDAT domain z–scores in children with kwashiorkor.

Table 4. Mother and child cooperativeness during MDAT assessment, by nutritional status (No, %)

Assessment	Affect of child	Engagement	Cooperativeness	Fear	Mother involvement
	Mostly sad	Uninterested	Very difficult	Too anxious	Passively watched
Marasmus	12 (25.0)	13 (27.1)	13 (27.1)	5 (10.4)	13 (27.1)
Kwashiorkor	14 (18.7)	20 (26.7)	20 (26.7)	5 (6.7)	23 (30.7)

Table 5. Background characteristics and Strengths and Difficulties Questionnaire scores by SAM and HIV status in children ≥24 month old

	SAM only* (n = 37)	SAM + HIV† (n = 14)	SAM + ND‡ (n = 15)
Group characteristics:			
Kwashiorkor (n, %)	33 (89.2)	8 (57.1)	9 (60.0)
Male (n, %)	20 (54.1)	8 (57.1)	11 (73.3)
Age in months (mean, SD)	37.6 (15.7)	42.7 (22.5)	50.8 (15.4)
Strengths and Difficulties Questionnaire (mean, SD):			
Emotional problems	2.1 (1.4)	3.1 (2.6)	2.6 (1.5)
Conduct problems	1.9 (1.5)	2.6 (1.8)	3.7 (1.5)
Hyperactivity–inattention problems	4.1 (1.5)	4.6 (1.0)	4.5 (0.9)
Peer problems	1.9 (1.5)	1.9 (1.7)	4.7 (1.6)
Prosocial behavior	3.2 (2.0)	3.2 (2.8)	0.1 (0.4)
Total Difficulties Score§	10.1 (4.2)	12.2 (5.5)	15.5 (3.8)
Impact supplement:			
Overall difficulties in emotions, concentration, behavior or being able to get on with other people? (n,%)	5 (13.5)	3 (21.4)	14 (93.3)

SAM – severe acute malnutrition, HIV – human infectious virus, SD – standard deviation, ND – neurodisability
*SAM only: 3 children missing.
†SAM + HIV group: children with both SAM and HIV: 1 child missing
‡SAM + ND group: children with both SAM and a pre–existing neurodisability: 2 children also were HIV positive.
§ANOVA analysis demonstrated a significant difference between the SAM only and SAM+ ND group (P<0.001) and between the SAM+HIV and SAM+CP group (P=0.048).

TDS score than the children with SAM Only (*P* < 0.001) or children with SAM+HIV (*P* = 0.048). We found no statistically significant differences in SDQ–TDS scores between the children with SAM Only and those with an HIV infection (*P* = 0.130). No calculations were done to examine the different subdomains between the different groups because of the small sample size.

DISCUSSION

We report on the severe developmental delays present in a well–characterized clinical population of children admitted with SAM to a nutrition rehabilitation unit in an African setting in a first study on this topic for decades. We have confirmed previous findings showing that SAM is associated with severe developmental delay. Moreover, our results indicate that there might be a significant difference in developmental attainment between children with kwashiorkor and with marasmus. Our study is unique in adding to the very sparse literature describing child behaviour as well as child development in young children with SAM.

In our study, children with kwashiorkor had a significantly worse language delay compared to children with marasmus at discharge. One explanation for this could be a difference in neurological involvement between kwashiorkor and marasmus. The striking neurological irritability of children with kwashiorkor has been identified as an important clinical feature [40]. However a recent case–report series did not reveal a difference in cerebral MRI findings between children with marasmus and kwashiorkor [41]. Secondly, the difference in language delay could be explained by a difference in the social environment between children with kwashiorkor and marasmus. Rytter et al. described lower breastfeeding rates in children with kwashiorkor, which might be related to decreased maternal care and stimulation [42]. Alternatively, the difference in language delay could be related to the differences in pathophysiology between kwashiorkor and marasmus. Recent evidence has linked the gut microbiome as being a causative factor in kwashiorkor [43]. Some have proposed that the immaturity of the gut microbiota (as seen in kwashiorkor) leads to the lack of production of important neurotransmitters and agents which are linked to brain development in children such as insulin–like growth factor (IGF–1) [44]. However studies comparing the microbiome of children with kwashiorkor and marasmus are still lacking.

Our study examined the child's social – emotional skills using direct observation (rated during the MDAT assessment) and with the use of two different questionnaires (MDAT social domain, SDQ). When examining the behaviour outcomes of children with SAM, we found different SDQ scores than previously reported in a World Bank evaluation of Malawian preschool (n = 1815) children attending community based childcare centres [34]. In the preschool group, the mean (SD) SDQ TDS was 13.9 (5.0) and the mean scores (SD) for the domains were: emotional problems (3.7 ± 2.3), conduct problems (3.0 ± 2.2), hyperactivity/inattention problems (4.5 ± 2.0), peer problems (2.6 ± 1.8) and the prosocial subscale (6.0 ± 2.4). Surprisingly, the mean SDQ TDS in the preschool children was higher than the mean SDQ TDS of the children in our study with SAM and SAM and HIV. In addition, the prosocial behaviour score was very low (3.2 ± 2.0) in children with SAM compared to the preschool children (6.0 ± 2.4), indicating a lack of sensitive behaviour in social interactions in our study population. An explanation might be that the children in our study did not demonstrate a high level of problematic behaviour because they were subdued and not very interactive indicated by the high level of children that were observed to be "not engaged" and "mostly sad" during our behaviour observation and the low MDAT social z–scores. The SDQ might not be the best scale to assess behavioural difficulties in children with SAM at discharge. Unfortunately our sample size was to small to investigate any differences in emotional and behavioural problems between children with kwashiorkor and marasmus. Additionally, our sample size might also have been too small to identify differences in our observation scale between marasmus and kwashiorkor.

Limitations of this study

Limitations of our study include its cross–sectional design and the assessment of developmental and problems only at discharge from the ward. We did not have any previous details about the development of the child before admission and no details about the home environment. Our findings regarding a significant difference in language delay between the children in the marasmus and kwashiorkor group might also have been explained by the age difference between both groups. The kwashiorkor children were significantly older although the MDAT z–scores are adjusted for age. Unfortunately, our sample size was determined by the main trial so for an age–stratified analysis our sample size was too small.
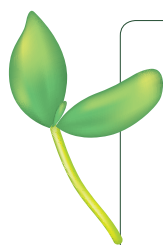
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It is likely that some developmental domains will continue to improve during the final few weeks of nutritional rehabilitation in the community [45]. This is especially true since WHO guidelines do not encourage using target–weight as hospital discharge criteria and admission to hospital is much shorter than it was a decade ago [21]. Despite clinical stabilization and improved appetite, children with SAM are still very brittle on discharge.

Our study has utilized a well–validated African developmental assessment tool, the MDAT, as an outcome measure however behaviour was measured using the SDQ, which has only been translated and not validated in Malawi. There are currently no SDQ cut–off scores available for Malawi, so it is unclear how many children with complicated SAM had SDQ scores in the clinical range. This may have led to a lack of significant results from this perspective. The five questions in the observation of child and maternal behaviour were not validated in this study and could have been confounded by how well the child performed on the MDAT test. Because our sample size was lower for children with marasmus, our power estimate was probably <0.80 to correctly identify a difference between children with marasmus and kwashiorkor.

Finally, we assessed only children with complicated SAM: these are by definition the most vulnerable and findings should not be directly extrapolated to the much wider group of children with uncomplicated SAM who are treated as outpatients under current protocols [46].

CONCLUSIONS

Findings from this study demonstrated that children with SAM have severe developmental delays after a hospital admission. Future research should focus on the longer–term developmental and behavioural follow–up outcomes of children with SAM in a Sub–Saharan African setting. These results demonstrate the need for developmental interventions during treatment of SAM in a hospital or community setting. Both McGregor's and Nahar's study identified significant differences in child development outcomes between children with SAM who received an intervention and children who did not. However, both studies were not randomized and had other limitations for example a high level of selection bias and attrition bias [47]. Therefore there is a high need for randomized intervention studies testing the efficacy, effectiveness and cost–effectiveness of various developmental support packages [48]. Our study identified a high proportion of children with pre–existing neurodisabilities (18%), future research should also investigate psychosocial interventions specifically targeted for these children. Developmental interventions need larger investments in staff and training to ensure that they are implemented and maintained in the many centres which see children with SAM to allow for the full development of these vulnerable children in order to improve future human capital and potential.

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Gap between contact and content in maternal and newborn care: An analysis of data from 20 countries in sub–Saharan Africa

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Background Over the last decade, coverage of maternal and newborn health indicators used for global monitoring and reporting have increased substantially but reductions in maternal and neonatal mortality have remained slow. This has led to an increased recognition and concern that these standard globally agreed upon measures of antenatal care (ANC), skilled birth attendance (SBA) and postnatal care (PNC) only capture the level of contacts with the health system and provide little indication of actual content of services received by mothers and their newborns. Over this period, large household surveys have captured measures of maternal and newborn care mainly through questions assessing contacts during the antenatal, delivery and postnatal periods along with some measures of content of care. This study aims to describe the gap between contact and content –as a proxy for quality– of maternal and newborn health services by assessing level of co–coverage of ANC and PNC interventions.

Methods We used Demographic and Health Surveys (DHS) data from 20 countries between 2010 and 2015. We analysed the proportion of women with at least 1 and 4+ antenatal care visit, who received 8 interventions. We also assessed the percentage of newborns delivered with a skilled birth attendant who received 7 interventions. We ran random effect logistic regression to assess factors associated with receiving all interventions during the antenatal and postnatal period.

Results While on average 51% of women in the analysis received four ANC visits with at least one visit from a skilled health provider, only 5% of them received all 8 ANC interventions. Similarly, during the postnatal period though two–thirds (65%) of births were attended by a skilled birth attendant, only 3% of newborns received all 7 PNC interventions. The odds of receiving all ANC and PNC interventions were higher for women with higher education and higher wealth status.

Conclusion The gap between coverage and content as a proxy of quality of antenatal and postnatal care is excessively large in all countries. In order to accelerate maternal and newborn survival and achieve Sustainable Development Goals, increased efforts are needed to improve both the coverage and quality of maternal and newborn health interventions.

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Over the past 25 years, concerted global efforts have led to dramatic reductions in maternal and under–five mortality. Globally, the maternal mortality ratio has declined by nearly 44%, [1] while the under–five mortality rate has fallen by 53% [2]. Yet, most low and middle income countries

failed to attain the maternal, newborn and child health goals set out in the Millennium Development Goals (MDGs) [3] and an unacceptably large numbers of women, newborn and children are still dying. About 800 women and 7700 newborns die each day from complications during pregnancy and child-birth and in the postnatal period [4]. Increasing newborn survival is a continuing challenge that must be addressed as neonatal deaths are becoming an increasing share of under–five deaths. [3]. Thus, a major unfinished agenda is the annual toll of 2.9 million neonatal deaths which account for 45% of all under–five deaths [5,6]. It is now well established that care around the time of birth has the potential to avert more than 40% of neonatal deaths and must be prioritized as the world seek to eliminate preventable neonatal deaths [7]. Key proven interventions include care by a skilled birth attendant, emergency ob-stetric care, immediate care for every newborn baby including breastfeeding support and clean birth prac-tices such as cord and thermal care and newborn resuscitation [2]. Evidence also suggests that increased coverage and quality of preconception, antenatal, intrapartum, and postnatal interventions by 2025 could avert 71% of neonatal deaths, 33% of stillbirths and 54% of maternal deaths per year [7].

Monitoring the coverage of effective and affordable maternal, newborn and child health interventions is central to assess progress [8,9]. For the purpose of global monitoring and reporting, a set of coverage in-dicators along the continuum of care have been adopted by global monitoring frameworks like the Glob-al Strategy for Women's, Children's and Adolescents' Health 2016–2030 and the Every Newborn Action Plan, to mention a few [10–12]. More women are now receiving antenatal care and delivering with a skilled attendant. Globally, antenatal care coverage for 4 or more antenatal visits by any provider has in-creased from 35% in 1990 to 58% in 2015 [13], while the proportion of births delivered with a skilled birth attendant rose from 61 to 78% between 1990 and 2015 [14]. However, these changes in coverage of maternal and newborn health have not reflected expected progress in impact indicators related to ma-ternal and newborn survival. It is being increasingly recognized that the global measures of coverage of maternal and newborn health capture only contacts with the health system with little information about the quality of care received. Maximizing coverage of measures focused on contacts alone is insufficient to reduce maternal, newborn and child mortality. To move towards elimination of preventable causes of ma-ternal and newborn deaths, increased coverage of recommended contacts should be accompanied by in-creased focus on content of services [4,15–21]. Recent evidence shows that closure of quality gap of fa-cility based maternal and newborn health services could prevent an estimated 113 000 maternal deaths, 531 000 stillbirths and 1.325 million neonatal deaths annually by 2020 [7].

Currently, the global indicators specific to pregnancy, delivery and postnatal periods that are common to the Global Strategy and ENAP include antenatal care (at least four visits), skilled attendant at birth and postnatal care for mothers and newborns within 48 hours following birth. These global maternal and newborn health indicators are truly the tip of the iceberg as these focus only on contacts between women or newborns with the health system and provide no indication of the content of services and quality of care delivered, which limits their usefulness for programmatic purposes [22]. A critical gap is noted in the measurement and reporting of quality of services received by women and children with the recom-mendation of adding core indicators assessing quality of maternal and newborn health care to the global coverage indicators [4,12,18,23,24]. Recently, the World Health Organization has proposed standards of care and measures assessing quality of maternal and newborn health care [4].

Large–scale, nationally representative household surveys such as UNICEF–supported Multiple Indicator Cluster Surveys (MICS) [25] and USAID–supported Demographic and Health Surveys (DHS) [26] are the largest source of data on maternal and child health outcomes at the population level. But, these sur-veys are limited in terms of providing information on content of care during the antenatal, labour, deliv-ery and postnatal period. Data are often collected on basic services received during antenatal care such weighing, testing of urine and blood, measuring blood pressure, tetanus protection, etc. During intra and postpartum periods, information on initiation of breastfeeding, weighing, immunization and postnatal care of mother and newborn is collected. While this information does not cover the breath of all services required, and especially in cases of emergency care and treatment, together, it can allow an assessment of whether women and newborns are receiving the minimum expected services. Thus, data collected through MICS and DHS has the potential to provide an indication of level of quality of care, at least at a basic lev-el. Unlike health facility or quality of care surveys that focus on care provided at service delivery sites, these household surveys have the advantage to provide nationally representative estimates that can also be disaggregated by relevant background characteristics including sub–national regions, mother's educa-tion, mother's age, sex of the child, wealth quintiles, etc., and allow to conduct relevant equity analyses which are a priority in the Sustainable Development Goals (SDGs) era.

In this paper, we analyse the co–coverage of content interventions used as proxy for quality of care received by women during antenatal care and by the newborn during postnatal period using data from nationally representative surveys. We then compare this co–coverage estimate with the global coverage indicators assessing contacts with health system to highlight the gap between contact and content.

METHODS

Data Source

Data for this study are from DHS surveys conducted between 2010 and 2015. We used data on interventions during the antenatal, delivery and postnatal periods from DHS surveys in 20 countries (see Table S1 in **Online Supplementary Document**). These 20 countries were included due to the availability of data on 8 antenatal care (ANC) and 7 postnatal care (PNC) interventions included in this analysis. Of the 20 countries, 18 countries had data on the full set of ANC interventions and 17 countries reported on all 7 PNC interventions included in the analysis.

Method of analysis

To assess the quality of maternal and newborn health services during pregnancy, birth and postnatal period, we analysed the co–coverage of selected interventions received by mothers and newborns. The co–coverage indicator, proposed in 2005, is a simple count of how many interventions are received by mothers and newborns out of a set of selected interventions [27].

For the purpose of this analysis, we included 8 ANC content interventions as a proxy for quality of antenatal care (**Table 1**). We first assessed the contact coverage estimates defined as (1) percent of women with a live birth in last 2 years who had at least one ANC visit with a skilled provider and (2) percent of women with a live birth in previous 2 years who had four or more ANC visits with at least one visit with a skilled health personnel. We then described coverage of content among all women with a live birth in previous 2 years and also restricted to women who reported having an ANC contact as the proportion of women with at least one ANC visit and those with four or more visits who received all 8 interventions.

In order to compare the gap between contact and content at the time of birth we included 7 PNC interventions. Interventions as weighing the newborn at birth, early initiation of breastfeeding, vaccinating the newborn with Polio dose 0 and BCG were included as proxy for quality as these are directly within the control of the skilled birth attendant. No prelacteal feeds for first 3 days was included as educating and assisting women on initiating exclusive breastfeeding and maintaining successful breastfeeding has been identified as a core function of skilled health personnel [28]. Postnatal health checks within 48 hours of birth for the mother and newborn was included due to lack of data availability on content of postnatal care in the analysed household surveys. For PNC, we analysed women delivering with a skilled birth attendant (SBA) whose surviving newborn received the 7 interventions. In the present analysis, a skilled birth attendant was identified based on the database maintained by UNICEF and Countdown which validates the skill and qualifications of the health personnel. For postnatal interventions, data on immunization was collected only on surviving children. We therefore, restricted the analysis to surviving children under 2 years at the time of the survey. This may positively affect the results if it is assumed that children who have died may be more likely to have had low quality care.

To assess the factors associated with the receipt of all interventions during ANC and PNC periods, we carried out random effect logistic regression on pooled data on women who had a contact. The regres-

Table 1. Set of interventions included for co–coverage analysis

8 INTERVENTIONS DURING ANTENATAL PERIOD	7 INTERVENTIONS DURING POSTNATAL PERIOD
1. Urine test	1. Newborn weighed at birth
2. Blood pressure taken	2. Early initiation of breastfeeding
3. Blood sample	3. No pre–lacteal feed during first three days of life
4. Iron supplementation	4. BCG vaccination
5. Tetanus protection	5. Polio vaccination at birth
6. Counselled on pregnancy complications	6. Postnatal care for newborn within 2 d of birth
7. Tested for HIV and received results	7. Postnatal care for the mother within 2 d of birth
8. Intermittent preventive treatment of malaria in pregnancy (IPTP)	

sion model controlled for several maternal, socio–demographic characteristics as maternal age, education status, parity, area of residence and wealth status.

RESULTS

Antenatal period

The analysis presented in **Figure 1** characterizes the quality of care received, among women who reported receiving at least one ANC visit with a skilled provider and those with four or more ANC visits. The gap between contact and content, defined as the difference between the percentage with four or more antenatal care visits and the percentage who received all 8 interventions, in the antenatal period is huge; compared to an average of 51% [range: 32%–76%] of women who received four or more ANC visits with at least one visit with a skilled health provider, only 5% (range: 0.3%–19%) of the women received all 8 ANC interventions (panel A in **Figure 1**). Among all interventions provided to women who had a contact during the antenatal period, receipt of three doses of intermittent preventive treatment of malaria in pregnancy was lowest (panel B in **Figure 1**). The gap between contact and content was found to be widest in case of Congo and Gabon where difference of 70 percentage points was noted between percentage of women who received 4+ ANC and the percentage of women who received all 8 ANC content interventions (see Table S2a in **Online Supplementary Document**).

The logistic regression analysis showed that women who had four or more ANC visits had 2 times higher odds of receiving all 8 interventions than those with only 1 ANC visit (odds ratio (OR)=2.06, 95% confidence interval (CI)=1.72–2.46). It was also found that primiparous women had 23% increased odds to receive all 8 ANC interventions compared to women with 5 or more children. The odds of receiving all ANC interventions increased significantly with greater levels of education and wealth status (**Figure 2**).

Postnatal period

The gap between contact and content of care highlights that though about two–thirds (65%, range: 34% to 93%) of women and newborns had contact with the health system only a handful are able to report receiving all 7 interventions considered (3%, range: <1% to 9%). (**Figure 3**). In the postnatal period, this gap was found to be the widest for Congo and Gabon. (see Table S2b in **Online Supplementary Document**).

As with ANC interventions, the likelihood of receiving all 7 PNC interventions was higher for newborns born to women with higher education (OR=1.23, 95% CI=1.12–1.35) and wealth status (OR=1.31, 95% CI=1.02–1.67). Contact during antenatal period was also found to be associated with the receipt of PNC interventions. Analysis revealed that the odds of newborns receiving all PNC interventions were 17% (OR=1.17, 95% CI=0.94–1.46) more for newborns whose mothers received four or more ANC visits than those who received 1–3 visits (**Figure 4**).
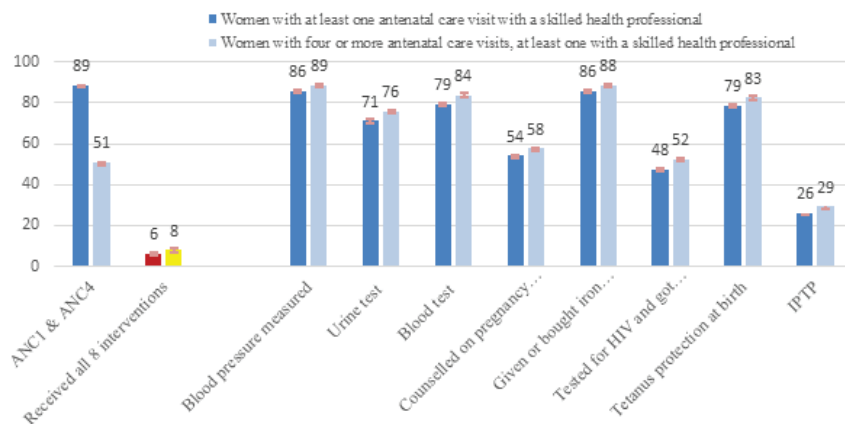
Figure 1. A. Percentage of women with a live birth in last 2 years receiving the complete set of 8 antenatal care (ANC) interventions; average across 18 countries, Demographic and Health Surveys (DHS) 2010–2015. The analysis included 18 countries as Burundi, and Rwanda did not have information about the full set of interventions. **B.** Percentage of women with at least one ANC visit and women with four or more visits by ANC intervention received; average across 18 countries, DHS 2010–2015. The analysis included 18 countries as Burundi, and Rwanda did not have information about the full set of interventions.
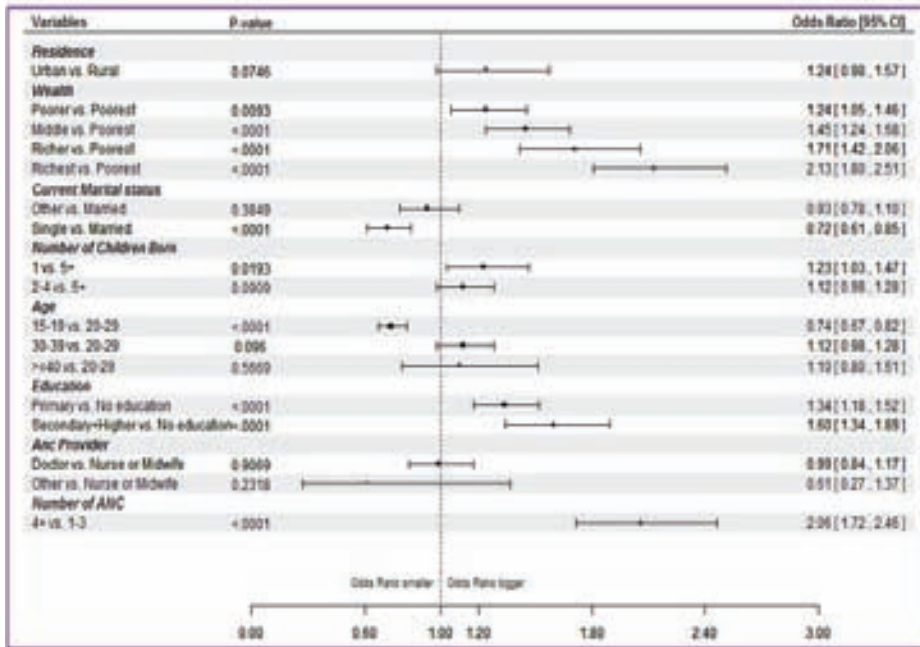
Figure 2. Odds ratios, 95% confidence intervals and p–values of receipt of all 8 antenatal care (ANC) interventions among women with antenatal contact from random effect logistic regression, (pooled Demographic and Health Surveys (DHS) data from 18 countries, DHS 2010–2014). The analysis included 18 countries as Burundi, and Rwanda did not have information about the full set of interventions.

Figure 3. Percentage of newborns/mothers by type of intervention received during postnatal period, average across 17 countries, Demographic and Health Surveys (DHS) 2010–2015. The analysis included 17 countries as Cameroon, Mozambique and Zimbabwe did not have information about the full set of interventions.
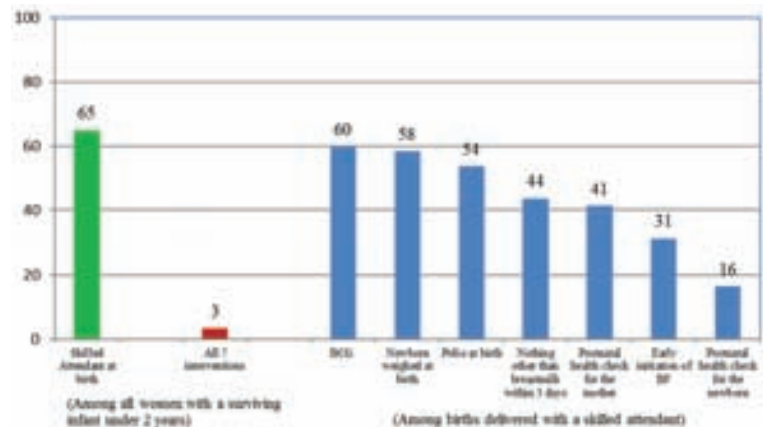
Figure 4. Odds ratios, 95% confidence intervals and p–values of receipt of all postnatal care (PNC) interventions from random effect logistic regression (pooled Demographic and Health Surveys (DHS) data from 17 countries, DHS 2010–2014). The analysis included 17 countries as Cameroon, Mozambique and Zimbabwe did not have information about the full set of interventions.
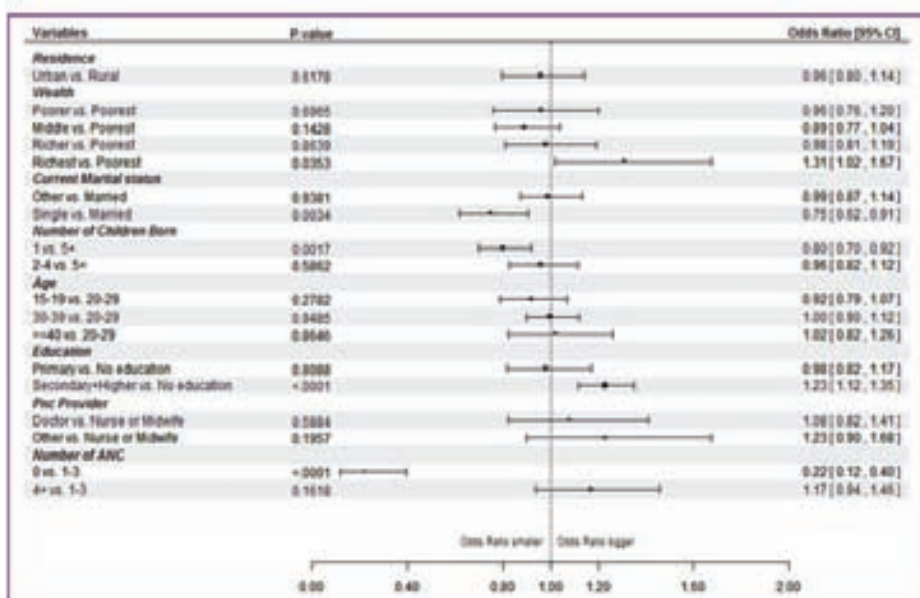
DISCUSSION

Our analysis demonstrates that there are large gaps between contact and content of care during antenatal, birth and postnatal period across all countries, as assessed using mother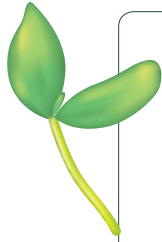s' recall from household survey. Among all ANC interventions included in the analysis, measurement of blood pressure was found to be the most commonly received intervention. Our finding resonates with an earlier study which assessed the content of antenatal care when data on antenatal interventions such as h8 and weight checking, blood pressure testing, and blood and urine testing was first available in Demographic and Health surveys [29]. The findings of the present study are also consistent with other studies that examined coverage of high quality contacts during the antenatal and postnatal period [24,29–31]. A recent study noted a substantial decline in the coverage of at least one antenatal contact and skilled birth attendance on adding content in Nigeria, Ethiopia and India [30]. Such gaps between globally recommended coverage indicators measuring contacts and actual content indicate ineffective care resulting in lack of accelerated progress towards maternal and newborn survival.

A limitation of this analysis is that we were able to analyse only interventions that were available in household surveys across the countries included in the analysis. We recognize that the scope of essential newborn care is broader and encompasses a range of interventions. Additional essential newborn care interventions such as thermal care and cord care have recently started to be included in household surveys. However, at the time of analysis data on additional newborn care interventions was available for only a few countries. Thus, our analysis included a subset of interventions in the antenatal and postnatal period for which data were available for a larger number of countries. Another limitation is that all measures included in the analysis are based on mother's recall of care during the antenatal and postnatal period and therefore may be subject to differential recall bias. Further, only few studies have assessed the validity of coverage indicators for MNCH interventions measured through household surveys. A recent series on "Measuring Coverage in MNCH" found that the sensitivity and specificity of coverage indicators is highly variable across interventions and women report less accurately about interventions that occurred immediately following childbirth [9].

An area of further research would be linking data from facilities surveys with population based data in order to better understand the quality of available services. Recent studies linking these two sources have found an association between service readiness in health facilities and the likelihood of receiving an appropriate set of essential newborn care interventions, as well as highlighted important gaps in service delivery as obstacles to universal access to health services [32,33]. The current global maternal, newborn and child health coverage indicators for pregnancy, labour and postnatal period focus merely on contacts with the health system with no information on quality and process of care. These measures of MNCH coverage only show whether services are reaching intended beneficiaries but do not assess the effectiveness or actual content of the care received. Our analysis establishes that focusing on merely contacts with health system rather than on content of care is a critical gap in assessing the true effectiveness of maternal and child health interventions. For example, we observed that although 2 in 3 births were attended by a skilled birth attendant, only 3% of the births received all 7 interventions recommended during the immediate postnatal period.

There is increasing evidence to support that increased coverage of recommended contacts alone is insufficient to reduce maternal and neonatal mortality and morbidity [4,7,15–21,24]. Quality of care is being internationally recognized as a critical aspect of the unfinished maternal and newborn health agenda [4,15]. Our findings also highlight the need to include elements of quality of care for regular monitoring through health management information systems (HMIS), household and facility surveys in other to identify the real gaps in effective coverage. Periodic program assessments can include a measure for content analysis of ANC and PNC visits in a given sample of mothers and newborns and explore reasons of omitting certain interventions which can vary from lack of competency to stock–outs of urine and haemoglobin test kits. Further research is also required to identify more sensitive indicators on quality of care and including these in future household surveys.

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Measuring postnatal care contacts for mothers and newborns: An analysis of data from the MICS and DHS surveys

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Background The postnatal period represents a vulnerable phase for mothers and newborns where both face increased risk of morbidity and death. WHO recommends postnatal care (PNC) for mothers and newborns to include a first contact within 24 hours following the birth of the child. However, measuring coverage of PNC in household surveys has been variable over time. The two largest household survey programs in low and middle–income countries, the UNICEF–supported Multiple Indicator Cluster Surveys (MICS) and USAID–funded Demographic and Health Surveys (DHS), now include modules that capture these measures. However, the measurement approach is slightly different between the two programs. We attempt to assess the possible measurement differences that might affect comparability of coverage measures.

Methods We first review the standard questionnaires of the two survey programs to compare approaches to collecting data on postnatal contacts for mothers and newborns. We then illustrate how the approaches used can affect PNC coverage estimates by analysing data from four countries; Bangladesh, Ghana, Kygyz Republic, and Nepal, with both MICS and DHS between 2010–2015.

Results We found that tools implemented todate by MICS and DHS (up to MICS round 5 and up to DHS phase 6) have collected PNC information in different ways. While MICS dedicated a full module to PNC and distinguishes immediate vs later PNC, DHS implemented a more blended module of pregnancy and postnatal and did not systematically distinguish those phases. The two survey programs differed in the way questions on postnatal care for mothers and newbors were framed. Subsequently, MICS and DHS surveys followed different methodological approach to compute the global indicator of postnatal contacts for mothers and newborns within two days following delivery. Regardless of the place of delivery, MICS estimates for postnatal contacts for mothers and newbors appeared consistently higher than those reported in DHS. The difference was however, far more pronounced in case of newborns.

Conclusions: Difference in questionnaires and the methodology adopted to measure PNC have created comparability issues in the coverage levels. Harmonization of survey instruments on postnatal contacts will allow comparable and better assessment of coverage levels and trends.

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The postnatal period, days and weeks following childbirth, is a vulnerable phase in the lives of mothers and newborns. Deaths within the first month of life represent 45% of all under–five deaths [1] and of these, far too many occur within the first week of birth. In 2015, nearly one million neonatal deaths occurred on the day of birth and close to two million newborns died in the first week of life [2]. Women too face an increased risk of morbidity and death after delivery. Maternal complications such as bleeding and sepsis following childbirth are responsible for over one–third of the maternal deaths worldwide [3]. To support mothers and newborns during this critical phase, postnatal care (PNC) was identified as a critical need by the World Health Organization (WHO) in 1997 [4]. In 2004, this recommendation was again highlighted in WHO's guidelines for pregnancy, childbirth, postnatal and newborn care [5]. Postnatal care guidelines were recently reviewed to recommend the number, timing and content of postnatal care contacts. WHO recommends the first postnatal contact within 24 hours of birth, followed by three additional contacts on day 3, between days 7–14 and six weeks after birth. In case of facility based deliveries, newborns should receive an immediate check at birth, full clinical assessment around one hour after birth and before discharge [6].

Recent research estimates that increased coverage of postnatal interventions, along with quality interventions from preconception to birth can save 1.9 million neonatal deaths annually. [7]. Postnatal care home visit from a trained provider within two days of delivery can lead to 30–40% reduction in neonatal mortality [8,9]. Given the significance of postnatal period and the effectiveness of postnatal care, it was essential that its coverage is measured and monitored at global and country level. In 2010, the countdown to 2015 called on the importance of developing and expanding the measurement and availability of data on PNC [10]. More recently with the launch of the United Nations Global Strategy for Women's, Children's and Adolescent's Health [11] and the Lancet Every Newborn Series in 2014 [12] the international community has agreed on new frameworks for global monitoring of MNCH targets. These recent frameworks which include Every Newborn Action Plan (ENAP) and Ending Preventable Maternal Mortality (EPMM) have included and prioritized postnatal care as a core coverage monitoring indicator.[11,13,14].

Although there is consensus on the importance of care during this period, the definition and measurement of PNC contacts with the mother and newborn have been a challenge. With regard to definition, an important issue described by the Newborn Technical Working Group deals with timing of postnatal care [15]. There is a lack of consensus among experts as to when the intrapartum period ends and the postnatal period begins. Other studies have analyzed the validity and reliability of respondents' answers regarding the timing of postnatal health check [16–18]. Timing of postnatal health check has typically ranged from minutes to days. Thus, many of these contacts may be part of the routine intrapartum care rather than distinct postnatal care contacts [15,16]. The confusion in the timing and content of PNC also led to further challenges in the measurement from household surveys. To measure, PNC, it is essential to convey appropriately a clear understanding to the respondent of what interventions are considered PNC, the timing, location (facility or outside facility) and provider of the interventions.

Large–scale, nationally representative household surveys such as the UNICEF–supported Multiple Indicator Cluster Surveys (MICS) [19] and the USAID–funded Demographic and Health Surveys (DHS) [20] now systematically collect data on PNC in their standard tools. Both survey programs report on the global postnatal care indicator for mothers and newborns which is defined as the "postnatal health check for the mother (or newborn) within two days of delivery". However, there are differences in the survey tools with MICS round four introducing a detailed module on PNC, tested in consultation with the Newborn Technical Working Group [15,21]. A couple of studies have raised the difference in MICS and DHS protocols along with their potential implications on MNCH coverage indicators, and called for greater attention to harmonizing the indicators [15,22]. With regards to PNC, there has not been a systematic assessment comparing the measurement approaches implemented by MICS and DHS, the two largest source of population–based MNCH coverage data in low and middle–income countries, so it has not been clear how questionnaire differences may affect the level and interpretation of PNC coverage.

The aim of the present study is to assess the data on postnatal care of mothers and newborns collected by MICS and DHS and compare PNC measures. In the first part of this paper, we compare the standard questionnaires of MICS and DHS. To illustrate and further study how differences in questionnaires may affect coverage levels, we then review the computation approach of the PNC coverage indicators in four countries with available data from both surveys.

DATA AND METHODS

Data

The data for this study come from standard individual women's questionnaires used in MICS and DHS. The questionnaires were obtained from the website of these survey progams [23,24]. The MICS survey program works in rounds and is currently in its round six. DHS is implemented in phases and is currently in its seventh phase. PNC questions are asked to women age 15–49 years with a last live birth in the recent past, generally the past two to five years. Questions are asked regardless of whether the child is still alive or not.

For the quantitative assessment of data on postnatal care, we first used estimates on postnatal care coverage within two days of delivery for women and children from all available DHS and MICS reports during the period 2010–2015. We then identified six countries that had a MICS and a DHS survey of the 60 countries with DHS and/or MICS during this period. The selection of six countries namely, Bangladesh, Ghana, Kyrgyz Republic, Malawi, Nepal and Zimbabwe was intended to be illustrative rather than representative of countries across the two survey programs. Out of these, we retained four countries because the DHS survey in Malawi and Zimbabwe in 2010 and 2011 respectively, did not collect all the required information on postnatal contacts of mothers and newborns. Survey sample sizes in the four countries examined are included in **Table 1**.

Statistical analysis

We first described the coverage of postnatal care within two days of delivery for mothers and newborn using all available and consistent data from MICS and DHS reports during the period 2010–2015. Then for each survey program, we reviewed the model questionnaires starting from four 4 for DHS and round three for MICS, when questions on PNC were first introduced in each programme. We examined the wording of the PNC questions asked to mothers and the reference populations used. We finally compared data collected on postnatal contacts using questionnaires from MICS round five and DHS phase 6 as these survey rounds had quantitative data available at the time of analysis and mapped the algorithm of measurement of postnatal contacts across the 2 survey programs. We could not include data from the latest MICS round six and DHS phase 7 surveys as no databases on these revised tools were available at the time of completion of this analysis. The observed difference in questionnaires was then used to investigate any difference in the PNC indicator values across the two survey programs.

Focusing on the four countries listed above, we then carried out a quantitative description of variables on postnatal contact and timing of health check from MICS and DHS data sets. To investigate sources of differences between surveys, we calculated coverage of any PNC separately for mothers and newborns and for facility and non–facility births, then distinguished "immediate checks" and "postnatal care visits". Immediate checks refer to women who gave birth in a health facility and who received a check before discharge or to women who gave birth outside a health facility in presence of a birth attendant (health professional or trained birth attendant) and who had a check before the attendant left. A "postnatal care visit" is considered occurring after discharge or after the birth attendant has left or any check for women who gave birth without an attendant. A postnatal health check refers to either of those checks and is accounted for in the measurement of the PNC indicator [25]. We then calculated the global indicator of postnatal care within two days after birth. The global indicator as reported in survey reports was calculated separately for institutional and non–institutional births by consistently excluding postnatal health

Table 1. Countries included in the analysis, data sources and sample sizes

Country	MICS			DHS		
	Year	Number of households	Number of women (15–49 years)	Year	Number of households	Number of women (15–49 years)
Bangladesh	2012–2013	55 120	29 599	2014	17 989	18 245*
Ghana	2011	12 150	10 963	2014	12 841	10 963
Kyrgyzstan	2014	7 190	6 995	2011	8 208	8 286
Nepal	2014	13 000	14 936	2011	11 353	12 918

DHS – Demographic and Health Surveys, MICS – Multiple Indicator Cluster Surveys

*Data was collected only on ever married women.

checks by a relative, family or friends. Our estimates for postnatal care of mothers and newborn differ from the survey report in case of Bangladesh DHS 2014 as the latter reports on postnatal health checks by only medically trained providers among live births in last three years while we follow a standardized approach of assessing postnatal care among live births in two years preceding the survey.

We then used the data collected in these 4 surveys to investigate the distribution of timing of health checks for mothers and newborns. Both survey programs report time of postnatal health checks in units of hours, days or weeks. However, for the purposes of this analysis, timing of postnatal health check was computed and assessed in terms of days, going from to 42 days.

Ethical review

Data used in this study come from publicly available data which are anonymized and therefore no ethical approval was sought. The Institutions that collected the data are responsible for securing the appropriate ethical approval prior to data collection.

RESULTS

PNC Coverage patterns

Figure 1 shows the coverage of postnatal care within two days for mothers and newborns, using all available consistent data from MICS and DHS surveys between 2010–2015. The figure compares PNC for mothers and newborns separately for DHS (A) and for MICS (B), and for different set of countries. The

A

B
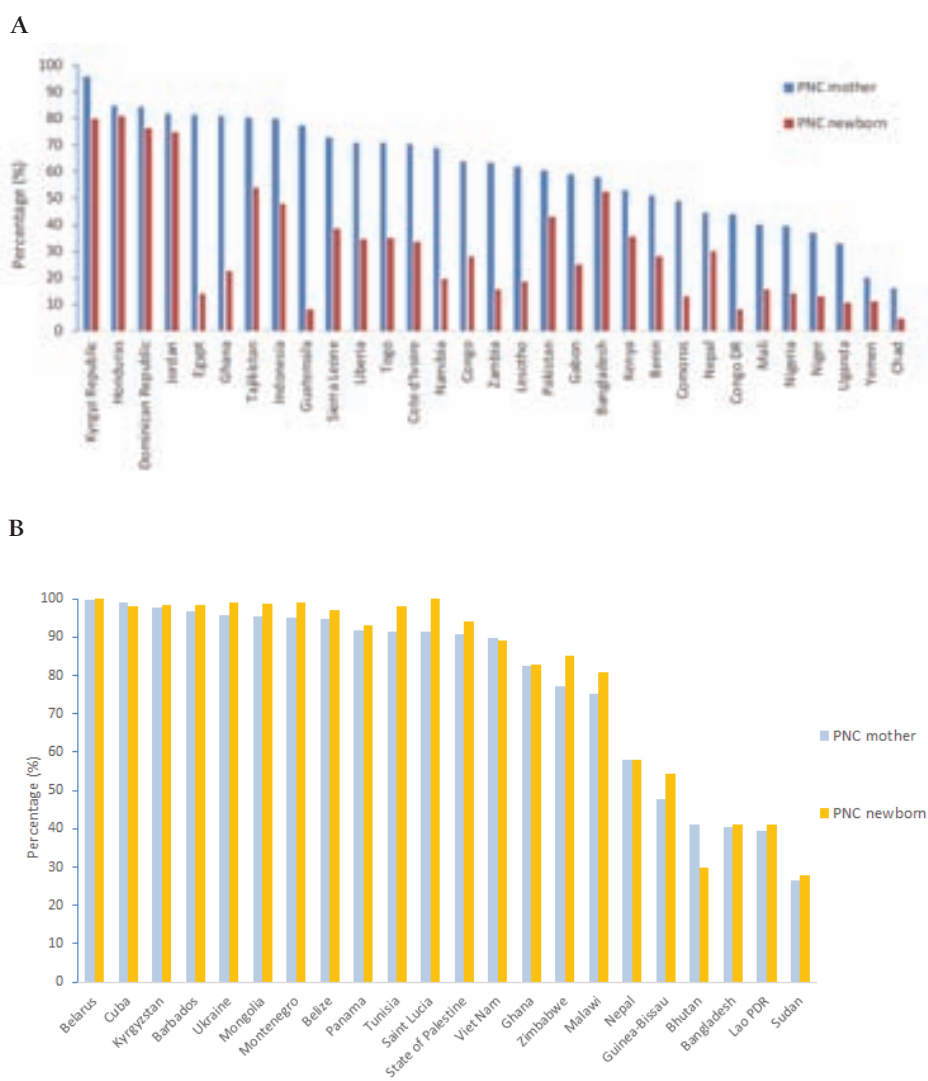
Figure 1. Coverage of postnatal care within two days of delivery for mothers and newborns, Demographic and Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS) (2010–2015). **A.** DHS data. **B.** MICS.

figure indicates variable levels of coverage across countries but highlights two important features. On the one hand, for DHS data, coverage levels of PNC appear higher for mothers than for newborns for all countries. On the other hand, for MICS, coverage of PNC appears fairly similar for mothers and for newborns, with newborns appearing to have a slight advantage over mothers in some countries (Tunisia, Saint Lucia, Zimbabwe and Malawi and Guinea–Bissau). The differential patterns between MICS and DHS persist in countries, such as Ghana and Kyrgyz Republic that had both types of surveys within the period examined.

Measuring PNC in DHS

Table 2 provides the evolution of introduction of PNC questions in DHS questionnaires by phase, and specific questions introduced. PNC questions were first introduced in phase 4 questionnaire in 1997. These questions were asked only to women who delivered outside a health facility. No attempts were made to measure PNC of newborns. In 2003, a new phase questionnaires were introduced (phase 5) which extended the PNC questions to all women regardless of place of delivery. In addition, questions on PNC for newborn were collected for the first time . However, they were asked only about facility births. From 2008, the phase 6 questionnaires extended PNC questions to all women and newborns, regardless of place of delivery. In addition, effort was made to ensure correct understanding of women's health check by the respondent by stating during the interview examples of actions that would be considered a health check.

The current phase 7 questionnaires introduced since 2013, continue to ask PNC questions of all women and newborns, but with additional questions to increase accuracy. Examples of what constitute a health check was provided for both women and newborns. Each category of respondents (ie, women with facility delivery who were checked before discharge, those who were not checked while in facility, and those who delivered outside a facility) has a separate set of questions investigating postnatal care for mothers and newborns. For the first time in this round, women who delivered and were checked in a health facility before discharge are once again asked questions about any check on health, time, provider and location of health checks following discharge to capture a subsequent postnatal health check. Similarly, questions about any postnatal health check of the newborn after discharge are asked of women with a facility delivery. As a result, the current phase of DHS may provide data on an additional postnatal health check for facility births. Another substantial addition in this round of survey is questions on content of PNC for mother and newborn. All women, whether they delivered in or outside a health facility are asked if a health care provider examined the cord, measured temperature, counseled on danger signs, and observed breastfeeding within two days of birth of the baby.

Measuring PNC in MICS

Table 3 describes measurement of PNC in MICS questionnaires. MICS introduced standard PNC questions in a module referred to as "Postnatal Health Checks" during the fourth round of the survey starting from 2009, although there were few prior surveys that had included limited PNC questions based on countries' specific initiatives. The MICS4 module collected detailed information on postnatal health contacts after delivery and distinguished an immediate health check from a postnatal visit for all mothers and births regardless of place of delivery. The module was developed following consultation with the New-

Table 2. Overview of PNC data collected in Demographic and Health Surveys (DHS)

	Phase 4 (1997–2003)		Phase 5 (2003–2008)		Phase 6 (2008–2013)		Phase 7 (2013–2018)	
	Facility births	**All home births**	**Facility births**	**All home births**	**Facility births**	**All home births**	**Facility births**	**All home births**
Postnatal care: Women								
Timing of 1st check	X	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Provider of 1st check	X	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Place of 1st check	X	Yes	Yes	Yes	No	No	Yes	Yes
Postnatal care: Newborn								
Timing of 1st check	X	X	X	Yes	Yes	Yes	Yes	Yes
Provider of 1st check	X	X	X	Yes	Yes	Yes	Yes	Yes
Place of 1st check	X	X	X	Yes	Yes	Yes	Yes	Yes
Content of check	X	X	X	X	X	X	Yes	Yes

X – Information not collected in the survey

Table 3. Overview of postnatal care (PNC) data collected in Multiple Indicator Cluster Surveys (MICS)

POSTNATAL CARE: WOMEN & NEWBORN	MICS 1–3 (1993–2009)	MICS 4 (2009–2013)			MICS 5 (2013–2016)			MICS 6 (2017–ONGOING)		
		Facility births	Assisted home births	Unassisted home births	Facility births	Assisted home births	Unassisted home births	Facility births	Assisted home births	Unassisted home births
Immediate check:										
Time of check	X	No	No	X	No	No	X	No	No	X
Provider of check	X	No	No	X	No	No	X	No	No	X
Place of check	X	Yes	Yes	X	Yes	Yes	X	Yes	Yes	X
Postnatal visit:										
Time of 1st visit	X	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Place of 1st visit	X	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Provider of 1st visit	X	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Content of PNC visit	X	X	X	X	X	X	X	Yes	Yes	Yes

X – Information not collected in the survey

born Indicators Technical Working Group, coordinated by Save the Children. Since MICS4, the PNC modules have been fairly consistent for both women and newborn. The latest round (MICS 7), initiated from 2017, introduced questions on PNC content, similar to the DHS questionnaires.

Implications for calculation of the global PNC indicator

Differences in the PNC questions between the two surveys programs have led to differences in the methodological approach used to compute the coverage of the PNC within two days after delivery, a potential source of incomparability (Table 4). To calculate this indicator, MICS distinguishes immediate check from PNC visits (post discharge or after attendant left in case of non–institutional deliveries) for mothers and newborns up to two days after delivery. A woman or newborn is then considered as having received PNC within two days after birth if an immediate check or a PNC visit occurred within these two days. DHS on

Table 4. Comparison of postnatal care (PNC) indicator measured in Demographic and Health Surveys (DHS) phase 6 and Multiple Indicator Cluster Surveys (MICS) round 4–6 questionnaires

DATA COLLECTED	DHS	MICS
Respondents:		
	Institutional births	Institutional births
	Non–institutional births	Non–institutional births with attendants
		Non–institutional births without attendants
Global indicator for postnatal care for mothers:		
Numerator	Number of women aged 15–49 years who received a health check within 2 days after delivery	Number of women aged 15–49 years who received a health check while in facility or at home following delivery, or a post–natal care visit within 2 days after delivery
Denominator	Total number of women aged 15–49 years with a live birth in the 2 years preceding the survey (**DHS changed reference period from five to two years**)	Total number of women aged 15–49 years with a live birth in the 2 years preceding the survey
Global indicator for postnatal care for newborns:		
Numerator	Number of last live births in the last 2 years who received a health check within 2 days after birth	Number of last live births in the last 2 years who received a health check while in facility or at home following delivery, or a post–natal care visit within 2 days after birth
Denominator	Total number of last live births in the last 2 years (**DHS changed reference period from five to two years**)	Total number of last live births in the last 2 years
First PNC contact	Unable to differentiate immediate health check from later postnatal visit	Able to distinctly assess and measure immediate health check from postnatal visit
Provider of first check	Yes	No, implied for institutional deliveries
Place of first check	Yes	Yes
Timing of first check	Yes	No
Duration of stay in facility	Yes	Yes
Postnatal visit	No	Yes, including timing, location and provider of first PNC visit
Content of PNC	Yes (starting in Phase 7)	Yes, starting in round 6

the other hand, does not make this distinction and includes only the first health check after delivery that may occur anytime between birth and two days following delivery, regardless of whether it was the immediate check or the later PNC visit (see Figure S1 and S2 in **Online Supplementary Document**). However, from phase 7 onwards DHS, questions separating out immediate check (pre–discharge check) from a later postnatal visit (post–discharge check) were introduced.

Assessment of the questionnaires from MICS 4 or 5 and DHS phase 6 further reveals that though the wording of questions about postnatal care of women are fairly similar across the two survey programs such as providing examples of a health check, a fundamental difference exists in the way questions are framed for postnatal care of newborns. While MICS asks about immediate health check and postnatal visits for the newborn without a specific reference period, DHS' questions on PNC for newborns considers checks within two months following the birth of the baby. However, in the most recent versions of the DHS (DHS phase 7) and MICS questionnaires, questions about postnatal care for women and newborns are closely aligned for institutional births but remain inconsistent for non–institutional births.

Comparing PNC coverage and timing between surveys

Table 5 and **Table 6** show measures of PNC respectively for women and newborns, comparing MICS and DHS results in the four countries. The pattern explained above, of broadly similar coverage of PNC for women between the two types of surveys and largely different coverage of PNC for newborns is seen in these four countries. Using MICS data, which allows us to distinguish between immediate (pre–discharge) checks and (post–discharge) postnatal visits, we see a higher proportion of newborns receiving a postnatal visit compared to women, while coverage of the immediate check is not very dissimilar for women and newborns.

In **Figure 2** and **Figure 3**, we assess the distribution of timing of health check for women and newborn in Ghana, respectively for DHS and MICS. From the
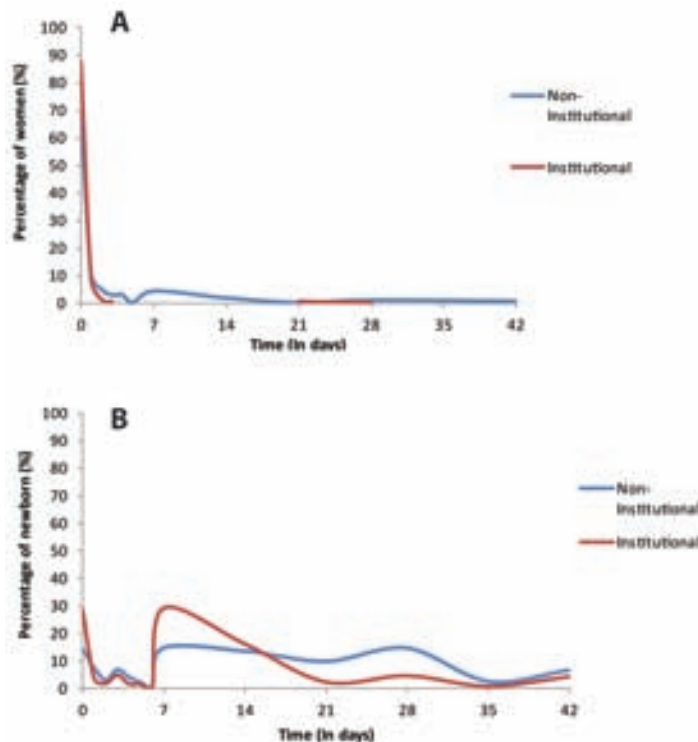
Figure 2. Timing of health check, Ghana Demographic and Health Surveys (DHS) 2014. **A.** Women. **B.** Newborn.

Table 5. Postnatal care for women across Demographic and Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS)

	BANGLADESH		GHANA		KYRGYZSTAN		NEPAL	
Women with non–institutional births:								
	DHS 2014	MICS 2012–13	DHS 2014	MICS 2011	DHS 2012	MICS 2014	DHS 2011	MICS 2014
n	1932	5391	572	825	5	11	1143	894
Any postnatal care	46.9	26.2	53.7	57.1	NR		13.7	20.6
Immediate health check	NA	22.1	NA	47.2	NA		NA	16.3
Postnatal visit	NA	8.7	NA	21.9	NA		NA	7.2
Postnatal health check within 2 d of delivery	42.4	24.5	44.9	50.9	NR		11.3	18.4
Women with institutional births:								
n	1272	2461	1691	1703	1686	1648	888	1130
Any postnatal care	92.7	78.4	95.9	97.7	98.5	99.2	88.5	90.6
Immediate health check	92.2	76.5	95.2	97.5	98.3	99.1	87.8	90.5
Postnatal visit	NA	17.8	NA	26.6	NA	55.6	NA	17.0
Postnatal health check within 2 days of delivery	86.8	76.9	93.4	97.5	96.3	99.1	87.3	90.6
All women (check within 2 days)	60.1	40.4	81.2	82.3	95.9	97.8	44.5	57.9

NA – question not asked, NR – analysis not reported due to small sample size

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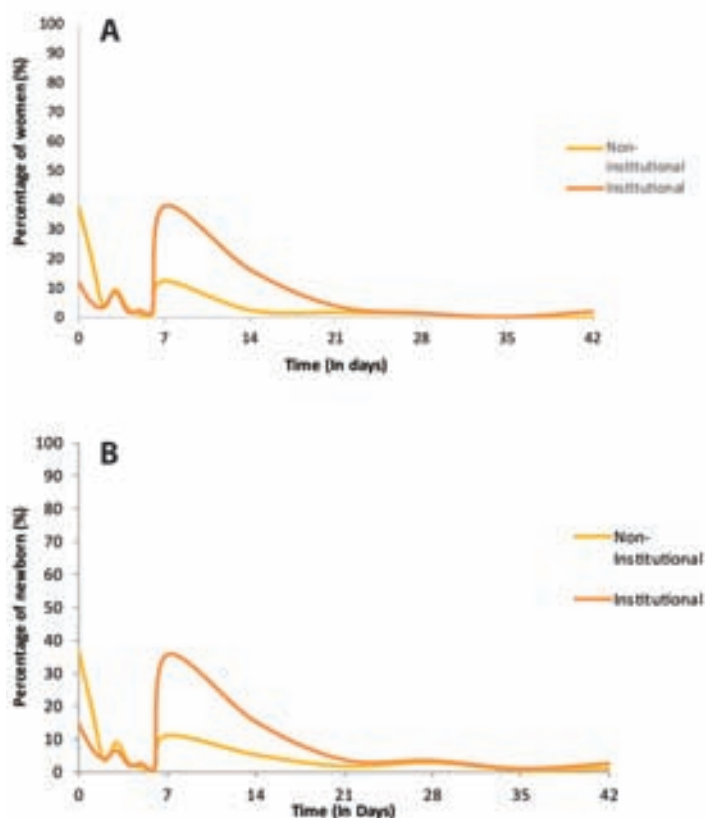
Figure 3. Timing of postnatal visit, Ghana Multiple Indicator Cluster Surveys (MICS) 2011. **A.** Women. **B.** Newborn.

DHS, most women appear to report a health check for themselves within the first days following delivery, most of the first day for institutional deliveries. However for their newborn, the reported coverage is much lower overall and the bimodal distribution (at day 0 and day 7) indicates that a substantial number of women report PNC on day 7 rather than within the first two days. For MICS, the figures include only the distribution of timing of the post–discharge or postnatal visit for women and newborn as the survey does not collect information on timing of immediate health check. The distribution of timing of postnatal visit is nearly identical for the mother and the newborn regardless of place of delivery.

DISCUSSION

Postnatal care is one of the essential strategies recommended for scale–up in many countries to improve health outcomes for women and newborn. The proportion of women receiving postnatal care within two days of delivery and the proportion of newborns receiving postnatal care within two days of delivery are the global consensus indicators for monitoring the coverage of this practice by countries. While enormous progress has been made in the past decade to accurately measure these indicators through household surveys, monitoring of levels and trend require consistent measurement across survey programs, time and geographies. We reviewed the way data on PNC indicators have been collected and the methodology used for their computation focusing on the two largest household survey programs, MICS and DHS. Results showed that the two survey programs have not measured the PNC indicator consistently, both in the way the questions are framed and the approach used for computation of this indicator. MICS dedicated a detailed standalone module to collect information on PNC for mother and newborn and included details that try to capture immediate checks following delivery from subsequent postnatal visit following discharge from health facility (in case of facility delivery) or when the attendant has left (in case of out–of facility deliveries with health professional or trained birth

Table 6. Postnatal care for newborn across Demographic and Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS)

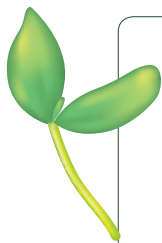|	BANGLADESH		GHANA		KYRGYZSTAN		NEPAL	
Non–institutional births:								
	DHS 2014	MICS 2012–13	DHS 2014	MICS 2011	DHS 2012	MICS 2014	DHS 2011	MICS 2014
n	1932	5391	572	825	5	11	1143	894
Any postnatal care	51.7	25.9	66.6	62.3	48.8	59.6	30.0	22.1
Immediate health check	NA	20.9	NA	47.4	NA	29.8	NA	15.0
Postnatal visit	NA	11.3	NA	35.9	NA	54.6	NA	11.7
Postnatal health check within 2 days of delivery	41.5	23.8	16.5	54.0	48.8	59.6	9.6	17.6
Institutional births:								
n	1272	2461	1691	1703	1686	1648	888	1130
Any postnatal care	81.7	83.3	73.4	97.9	89.5	99.9	68.5	91.2
Immediate health check	NA	80.5	NA	97.1	NA	99.7	NA	90.6
Postnatal visit	NA	26.6	NA	44.3	NA	94.9	NA	22.3
Postnatal health check within 2 days of delivery	74.3	80.9	24.9	97.1	80.0	99.7	56.5	90.6
All births (check within 2 days)	54.5	41.2	22.8	83.1	79.8	98.5	30.1	57.7

NA – question not asked, NR – analysis not reported due to small sample size

attendant). Their approach and questions used are similar for mothers and newborns. The calculation approach of the PNC indicators for either mothers or newborns thus captures occurrence of an immediate and/or a later postnatal visit occurring within the two–days window. By segmenting the postnatal period, this approach aims to better trigger the memory of the respondent toward a more accurate response. Consequently, coverage levels based on this approach tend to be higher than that of the DHS, and similar for both women and newborns.

DHS, on the other hand, implements a blended pregnancy and PNC module and measures the indicator differently for mothers and newborns. It does not systematically distinguish the immediate vs postnatal visit. Furthermore, for newborns, PNC questions in DHS refer to a check in the two month period following birth. The resulting coverage measures show a much lower PNC rate for newborns compared to women. We suspect that when mothers are asked during interviews about PNC of their newborn within the two months following the delivery, they are more likely to recall the most recent visit, which is likely to fall outside the first two days, resulting in an under–estimation of the coverage indicator. We indeed found a divergence in the distribution of timing of postnatal checks in DHS, with women reporting most immediate care for themselves (thus resulting in high coverage of PNC) while for their newborn, a substantial number of women tend to report the check at day 7, resulting in lower coverage of PNC within two–day of delivery for newborns. Because such two–month reference window is not applied to women themselves, they are likely to report more accurately a check that occurred within two days of delivery, especially given pre–discharge questions were specified. However, the confusion between when the intrapartum period ends and the postnatal period begins means that the immediate health check may also be capturing immediate intrapartum checks not necessarily considered as postnatal health check. A qualitative study in Malawi and Bangladesh suggested that women may potentially be reporting on a routine intrapartum check rather than a distinct postnatal contact [15,16]. This may result in overestimation of PNC measures in women for DHS and in both women and newborns for MICS.

While our analysis does not constitute a validation of one approach vs the other, a clear and most actionable implication is for MICS and DHS to coordinate and align the measurement of such critical indicators to improve comparability between measures coming from the two survey programs. Until such alignment occurs, measures produced will not be comparable. There are also increasing calls for going beyond measures of contact such as PNC to incorporate measure of content interventions received by mothers and newborns during these contacts [26,27]. A simple measure of contact does not provide any indication of the quality of care received, the duration and contents of such contacts. The most recent MICS round 6 and DHS phase 7 have both included a number of questions on the content of the first check within the first 2 days following birth, including cord examination, weight and temperature assessment, breastfeeding counseling and observation and counseling on symtpoms that cause a mother to take a newborn to health care. These efforts must also be guided by clear recommendation from the maternal and newborn community on content of PNC and its quality. The recent revisions to the DHS and MICS tools to improve alignment in the measurement of PNC indicators and incorporate information on PNC content is a welcome step toward filling these data gaps. However, the currents tools are still not fully aligned on PNC measurement, especially for out–of–facility deliveries.

Furthermore, more studies must to be carried out to validate reports from mothers on intrapartum and postpartum care during household survey to help fine tune the measurement tools.

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Evidence from household surveys for measuring coverage of newborn care practices

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Background Aside from breastfeeding, there are little data on use of essential newborn care practices, such as thermal protection and hygienic cord care, in high mortality countries. These practices have not typically been measured in national household surveys, often the main source for coverage data in these settings. The *Every Newborn* Action Plan proposed early breastfeeding as a tracer for essential newborn care due to data availability and evidence for the benefits of breastfeeding. In the past decade, a few national surveys have added questions on other practices, presenting an opportunity to assess the performance of early breastfeeding initiation as a tracer indicator.

Methods We identified twelve national surveys between 2005–2014 that included at least one indicator for immediate newborn care in addition to breastfeeding. Because question wording and reference populations varied, we standardized data to the extent possible to estimate coverage of newborn care practices, accounting for strata and multistage survey design. We assessed early breastfeeding as a tracer by: 1) examining associations with other indicators using Pearson correlations; and 2) stratifying by early breastfeeding to determine differences in coverage of other practices for initiators vs non–initiators in each survey, then pooling across surveys for a meta–analysis, using the inverse standard error as the weight for each observation.

Findings Associations between pairs of coverage indicators are generally weak, including those with breastfeeding. The exception is drying and wrapping, which have the strongest association of any two interventions in all five surveys where measured; estimated correlations for this range from 0.47 in Bangladesh's 2007 DHS to 0.83 in Nepal's 2006 DHS. The contrast in coverage for other practices by early breastfeeding is generally small; the greatest absolute difference was 6.7%, between coverage of immediate drying for newborns breastfed early compared to those who were not.

Conclusions Early initiation of breastfeeding is not a high performing tracer indicator for essential newborn care practices measured in previous national surveys. To have informative data on whether newborns are getting life–saving services, standardized questions about specific practices, in addition to breastfeeding initiation, need to be added to surveys.

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Every year, 2.7 million babies die during the first month of life, largely from preventable causes [1]. The World Health Organization has prioritized several newborn care practices that could be used at home or facility to prevent many of these unnecessary deaths – thermal care to prevent hypothermia, hygienic cord and skin care to prevent infections, and early and exclusive breastfeeding [2]. Strong evidence on the mortality impact

of specific practices is mostly unavailable, but the benefits are likely substantial. Delphi–based expert panels suggested clean postnatal practices could reduce deaths due to infections by 40% [3] and thermal care could reduce deaths due to preterm complications by 20% [4]. More robust evidence exists for the impact of early and exclusive breastfeeding, with a recent cohort trial finding late breastfeeding initiators had higher neonatal mortality (41% if initiated 2–24 hours after birth, 79% if more than 24 hours after birth) and infant mortality, which persisted even in exclusively breastfed babies, suggesting both early and exclusive breastfeeding independently reduce mortality [5].

Despite the importance of these behaviors, most countries do not have coverage data to know if they are practiced. Very few national health information systems collect data on these practices [6] and national surveys, such as the Demographic and Health Survey (DHS) and the Multiple Indicator Cluster Survey (MICS), usually only include questions on breastfeeding, but not other newborn care practices [7]. The *Every Newborn* Action Plan's (ENAP) Measurement Improvement Roadmap [8] was an important step forward in building momentum for improving measurement on newborn care, though mainly focused on coverage indicators for interventions to manage small or sick newborns, such as Kangaroo Mother Care and infection management. ENAP proposed early breastfeeding as a tracer for essential newborn care—preventive and supportive care all newborns need—due to the strong evidence for breastfeeding and its availability from DHS and MICS. However, the correlation between breastfeeding and use of other newborn care practices has not been examined, so it is not known if breastfeeding coverage corresponds with coverage of other practices. In the absence of data, it is generally assumed coverage of these practices is low in settings with high neonatal mortality. For example, a recent effort to model the impact of improving coverage of various interventions in high–burden countries assumed baseline coverage of clean postnatal practices and simple thermal were each just 11%, while coverage of exclusive breastfeeding at one month was estimated to be 62% (early initiation was not included) [4]. The lack of coverage data for other practices makes it difficult to monitor the effectiveness of strategies to promote them or identify un–reached populations [9].

Population–based household surveys, particularly DHS and MICS, are often the main source for intervention coverage data in low– and middle–income countries. In many of these countries, a large proportion of deliveries occur outside health facilities and routine data systems are often weak [10]. Surveys are also used to collect sociodemographic data to identify inequities [11,12]. DHS and MICS measure contacts with the health system during the antenatal, birth, and postnatal periods, but contacts alone are poor indications of the content and quality of care and should not be used as a stand–in for effective coverage of high impact interventions [13,14]. Of the essential newborn care practices, only breastfeeding questions were included in standard DHS and MICS questionnaires until 2016. However, surveys are adapted to each country and a few national surveys prior to 2016 included additional questions on newborn care, presenting an opportunity to assess the performance of breastfeeding initiation as a tracer for essential newborn care practices.

This study first examines how DHS and MICS from 2005–2014 have asked about newborn care practices and standardizes the calculation of indicators, to the extent possible, to examine and compare coverage levels across countries. We then investigate the utility of early initiation of breastfeeding as a tracer indicator for essential newborn care. This analysis is especially important as countries weigh the need to include additional questions on newborn care into their next national survey. While both DHS and MICS recently included additional standardized newborn indicators in their model questionnaires based on global consensus around indicators that could be collected in household surveys (**Table 1**), most questions are optional and countries must choose to include them [15,16].

METHODS

We reviewed publicly available DHS and MICS reports from 2005–2014 to identify surveys capturing newborn care practices in addition to breastfeeding. Once surveys were identified, analysis proceeded with two primary components, the first descriptive and the second to examine relationships between indicators of coverage. Twelve national surveys in eight countries (four in South or Southeast Asia, three in sub–Saharan Africa, one in western Asia) were found that measured at least one indicator for immediate newborn care in addition to initiation of breastfeeding. Three countries (Bangladesh, Nepal, and Armenia) had more than one survey and therefore the potential to compare coverage over time. **Table 2** briefly describes all twelve surveys by the number of births recorded in the two years prior to each survey, the proportion of births occurring in non–institutional settings, and the proportion of Caesarean births. We

Table 1. New questions in DHS (Phase 7) and MICS6 related to newborn care practices

DHS Women's Model Questionnaire:
434 Immediately after the birth, was (NAME) put on your chest?
434A Was (NAME)'s bare skin touching your bare skin?
DHS Optional Newborn Module:
NB1 Was (NAME) wiped dry within a few minutes after birth?
NB2 How long after the birth was (NAME) bathed for the first time?
NB3 CHECK PLACE OF DELIVERY
NB4 What was used to cut the cord? (non–institutional births only)
NB5 Was it new or had it ever been used before? (non–institutional births only)
NB5A Was it boiled before it was used to cut the cord? (non–institutional births only)
NB6 Was anything applied to the stump of the cord at any time?
NB7 What was applied?
CH1 CHECK SUBSTANCES APPLIED TO CORD
CH2 Was chlorhexidine applied to the stump at any time?
CH3 How long after the cord was cut was chlorhexidine fist applied?
CH4 For how many days was chlorhexidine applied to the stump?
CH5 How many times per day was chlorhexidine applied to the stump: once a day, twice a day, three times a day, or four or more times a day?
MICS6 Questionnaire for Individual Women:
MN23 Immediately after the birth, was (*name*) put directly on the bare skin of your chest? [WITH PHOTO OF SKIN–TO–SKIN POSITION]
MN24 Before being placed on the bare skin of your chest, was the baby wrapped up?
MN25 Was (*name*) dried or wiped soon after birth?
MN26 How long after the birth was (*name*) bathed for the first time?
Recommended only for countries with high NMR, large programs on cord care, large proportion of non–facility births:
MN27 Check MN20: Was the child delivered in a health facility?
MN28 What was used to cut the cord? (non–institutional births only)
MN29 Was the instrument used to cut the cord boiled or sterilised prior to use? (non–institutional births only)
MN30 After the cord was cut and until it fell off, was anything applied to the cord?
MN31 What was applied to the cord?

Table 2. Twelve nationally representative household surveys that included measures of essential newborn care beyond breastfeeding

Country	Year	Type	Number of Households Surveyed	Number of births in past two years	Number (%) of non–institutional births in past two years	Number (%) of cesarean births in the past two years
Armenia	2005	DHS	4022	621	8 (1%)	59(10%)
Armenia	2010	DHS	3535	675	1 (0%)	90(13%)
Bangladesh	2007	DHS	8583	2469	1949 (79%)	262(11%)
Bangladesh	2011	DHS	14068	3483	2337 (67%)	648(19%)
Bangladesh	2014	DHS	14228	3283	1932 (59%)	805(25%)
Ghana	2014	DHS	6062	2517	698 (28%)	282(11%)
India	2005	DHS	76010	20837	9585 (46%)	2438(12%)
Malawi	2014	MICS	20772	7576	563 (7%)	412(5%)
Nepal	2006	DHS	6672	2270	1817(80%)	58(3%)
Nepal	2011	DHS	7874	2103	1156(55%)	127(6%)
Nigeria	2013	DHS	23364	13570	8345(61%)	326(2%)
Timor–Leste	2009	DHS	7516	4006	3107(78%)	74(2%)

DHS – Demographic and Health Survey, MICS – Multiple Indicator Cluster Survey

compared how questions were asked in different surveys based on the following criteria: 1) wording of questionnaire items, 2) how responses were quantified, 3) target population of interest (eg, facility or home births), 4) reference period (eg, in the two or three years preceding survey), and 5) birth subset (all births in reference period or only most recent birth).

We estimated coverage of newborn care practices as defined by each survey, and then, to the extent possible, standardized indicators across surveys. Our standardized indicators are defined in Table 3, which also shows the comparability of these definitions to data that will be collected with the new DHS and MICS questionnaires. Given differences in wording and answer options, indicator numerators could not

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Table 3. Standardized definitions of newborn coverage indicators used for this analysis and comparability to DHS (Phase 7) module and MICS6

Indicator group	Standardized definition	Comparability to DHS (Phase 7)	Comparability to MICS6
Breastfeeding initiation	Put to breast within one hour of birth	Comparable	Comparable
Thermal care	Dried within five minutes of birth OR before delivery of the placenta	Somewhat comparable DHS does not reference exact time or delivery of placenta' to 'DHS does not use five minutes or delivery of placenta for time reference	Somewhat comparable (MICS6 does not reference exact time or delivery of placenta' to 'MICS6 does not use five minutes or delivery of placenta for time reference)
	Wrapped within five minutes of birth OR before delivery of the placenta	Not comparable (not collected in DHS)	Not comparable (MICS6 asks if baby wrapped up before placed on mother's bare chest.)
	Neonate put on the belly or breast before delivery of the placenta OR directly on the bare skin of your chest	Somewhat comparable (DHS specifies bare skin must be touching in 2 questions)	Somewhat comparable (MICS specifies bare skin must be touching in 2 questions and a photo)
	Not given a bath in the first 24 h after birth	Comparable	Comparable
Hygienic cord care	A new or sterilized (boiled) instrument was used to cut the umbilical cord, or a clean delivery kit was used	Somewhat comparable (DHS does not ask about clean delivery kit)	Somewhat comparable (MICS6 does not ask about clean delivery kit)
	No substance was applied to the umbilical cord after it was cut	Comparable	Comparable

DHS – Demographic and Health Survey, MICS – Multiple Indicator Cluster Survey

be perfectly harmonized across surveys. For example, the timing of interventions was recorded as an exact amount in some surveys, and as timing relative to other events in other surveys.

We standardized indicator denominators by recall period and population, using the shortest reference period across surveys (last birth in the two years preceding survey), and the smallest common reference population (births that were delivered at home). We used these standard populations and definitions to estimate coverage, accounting for strata and the multistage survey design in each case [17,18]. Once we standardized these coverage estimates, we examined their levels across countries and across time for multiple surveys in a single country.

We then examined the associations between various coverage indicators among those surveyed to determine how well early breastfeeding functions as a tracer for other indicators of newborn care. We used Pearson correlations to describe associations between each pair of estimated coverages [19]. We expected *a priori* that some types of coverage would be positively correlated: that is, an infant receiving a specific intervention would be likely to receive a related intervention (for example, an infant who is dried may often be wrapped as well). We also hypothesized some coverages would be negatively correlated, indicating that an infant would be less likely to receive an intervention if another intervention had been received (for example, wrapping and placing skin–to–skin). We examined relationships with breastfeeding within one hour of delivery for each indicator at the individual level with these correlations.

We also aimed to describe the coverage of newborn care practices among newborns breastfed early and examine if it differed from coverage among newborns who did not breastfeed early. For each survey, we stratified by breastfeeding within one hour, and compared coverage estimates for each group. We statistically determined the difference between the coverage of newborn care practices for these groups. We then pooled observed differences across surveys in a meta–analysis. In order that different surveys contribute to the estimate overall, we used the inverse standard error as the weight for each observation. Using inverse standard errors as weights allows survey estimates with more uncertainty to contribute less information to overall estimates, per standard meta–analysis protocol. [20].

RESULTS

Two surveys (Nepal 2011 and Nigeria 2013) measured all seven indicators considered for the second part of our analysis (**Table 4**). Surveys in Armenia and Ghana each only collected one indicator of interest other than breastfeeding. The India 2005 survey included multiple newborn care practices, but asked as a composite question so it is not possible to tease out coverage of each practice. Except for early breast-

Table 4. Immediate newborn care indicators included for each of twelve recent surveys

Indicator	ARMENIA 2005	ARMENIA 2010	GHANA 2014	INDIA 2005	MALAWI 2014	BANGLADESH 2007	BANGLADESH 2011	BANGLADESH 2014	NEPAL 2006	NEPAL 2011	NIGERIA 2013	TIMOR–LESTE 2014
Breastfed within first hour	A	A	A	A	A	A	A	A	A	A	A	A
Dried				H	H	H	A	H	H	H	H	H
Wrapped			A	H		H	A		H	H	H	
Bathed after 24 h				H	H	H	H	A	H	H	H	H
New or boiled blade				H	H	H	H	H	H	H	H	H
Nothing applied to cord				H	H	H	A	H	H	H	H	H
Skin to skin or baby put on mother's belly or chest	A	A						A		H	H	

A – Surveys that collected data for all non– Caesarean last births, H – Surveys that collected data only for home births

feeding, coverage for other practices was often measured only for home births. However, in Armenia, Ghana, Malawi, and Bangladesh (2007 and 2014), some items were measured for all non–Caesarean births. Questions and response categories for each survey can be found in Table S1 in **Online Supplementary Document** and respective coverage estimates from official survey reports in Figure S1 in **Online Supplementary Document**, though coverage is generally not comparable across surveys due to question wording, their reference populations, and time periods. We excluded four surveys from further analysis given the limited amount of comparable indicators – Armenia (2005 and 2010), Ghana, and India – leaving eight surveys for standardized coverage measurement.

We used the standardized definitions for most recent births which were also in non–institutional settings in the two years preceding the survey. Resulting coverage estimates are shown with 95% confidence intervals in **Figure 1** and Table S2 in **Online Supplementary Document**. Using a new or boiled instru-
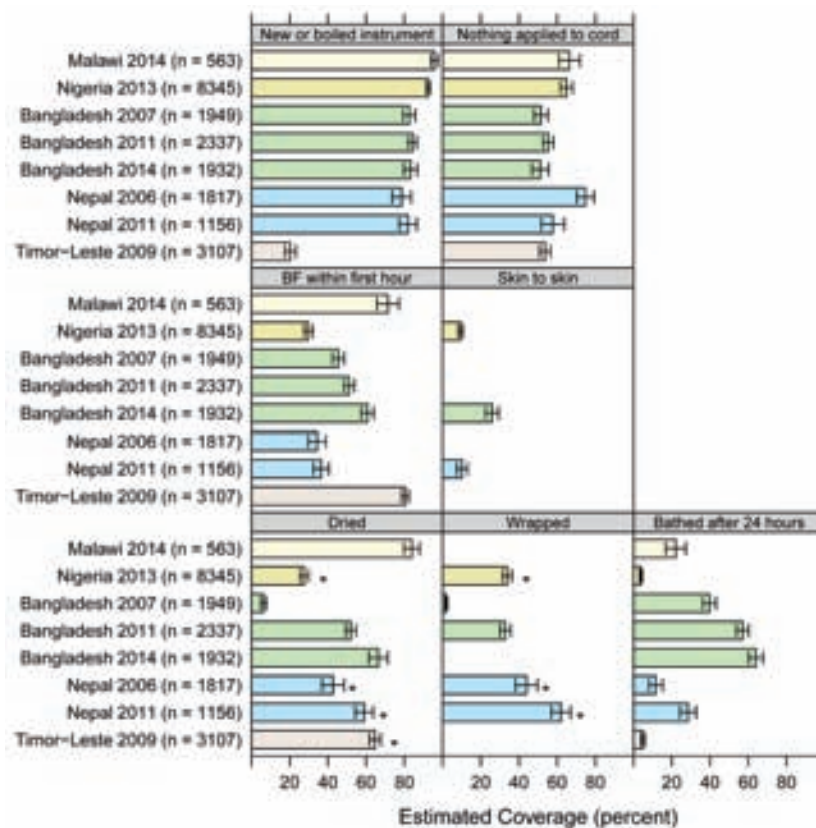
Figure 1. Standardized coverage estimates for eight national surveys, with 95% confidence limits, for most recent births that were delivered in non–institutional settings in the two years preceding survey. Asterisk indicates that "before placenta delivery" was used for time reference, as opposed to "within five minutes" for drying or wrapping.
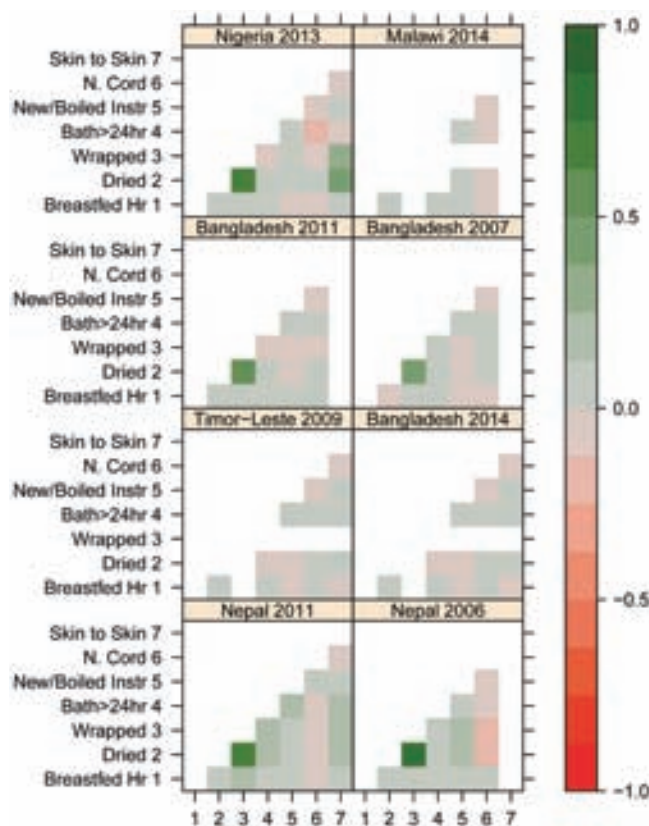
Figure 2. Correlation matrices for eight national surveys and seven standardized coverage indicators, for most recent births in the two years preceding survey that were delivered in non–institutional settings. Strong correlations are indicated by dark green, negative correlations are indicated by red.

ment to cut the umbilical cord is generally the highest estimated coverage, except in Timor–Leste. Placing the baby skin–to–skin or on the mother's belly or chest was measured in only three of the eight surveys and generally had the lowest estimated coverage among the newborn care practices. Some measures had wide variation across surveys, such as drying, which ranges from 6.3% in Bangladesh (2007) to 84% in Malawi (2014). Trends in coverage over time can also be inferred from **Figure 1** for the two countries with more than one survey. Drying, wrapping, and delayed bathing increased in both Bangladesh and Nepal. There is no apparent change over time in using a new or boiled instrument in either country. Nepal had no change in early breastfeeding, but Bangladesh had a small increase between 2007 and 2014. For no application to the cord, there is a decline of 17 percentage points (95% confidence interval 6.8–28.0) in Nepal from 2006 to 2011. The 2011 survey added a follow–up question on what was applied to the cord with chlorhexidine as an answer option. Yet chlorhexidine use fails to explain this decrease in dry cord care: changing the 2011 coverage indicator to include nothing *or* chlorhexidine applied resulted in little change in the 2011 coverage estimate (only 1% respond regarding chlorhexidine, so coverage changes from 57.7% to 58.7%). Coverage for dry cord care was unchanged over time in Bangladesh.

We used these standardized coverage estimates in each survey to examine the associations between different newborn care practices at the individual level, to see whether neonates who receive a specific intervention are likely to receive another. We estimated the Pearson correlation between coverage indicators for each survey for all available measurements. The resulting associations are shown in **Figure 2** as a map, where interventions that tend to occur together are darker green the more they are positively correlated, and interventions that tend to occur separately are darker red the more they are negatively correlated. (See Table S3 in Online **Supplementary Document** for correlations.) Associations between pairs of newborn coverage indicators are generally weak, including those with breastfeeding. The exception is for drying and wrapping, which have the strongest association of any two interventions in all five surveys where they were measured, with an estimated correlation of 0.65 in Nigeria 2013; 0.83 and 0.73 in Nepal 2006 and 2001, respectively; and 0.47 and 0.58 in Bangladesh 2007 and 2011. Other correlations above 0.2 are between being placed "skin–to–skin" (includes babies placed mother's belly or chest in Nigeria and Nepal, babies placed on the mother's bare skin in Bangladesh) and both drying and wrapping in Nigeria 2013 and Nepal 2011. In Nigeria, infants placed "skin–to–skin" are somewhat more likely to have been dried (correlation 0.42) and wrapped (correlation 0.35). In Nepal 2011, infants placed "skin–to–skin"

are also more likely to have been dried (correlation 0.24) and wrapped (correlation 0.23). Skin–to–skin and drying were not related in Bangladesh 2014 (correlation 0.013), while wrapping was not asked.

In addition to these associations, we stratified surveys by early breastfeeding and examined the differences in coverage for those with early breastfeeding compared to those who did not breastfeed early. The estimated contrasts in coverage are shown for each survey and pooled across surveys in **Table 5**. The contrast in coverage between neonates by early breastfeeding is generally small, with pooled differences less than seven percentage points for each indicator. The absolute difference in coverage of essential practices between newborns breastfed early and those who were not ranged from less than one percent for having nothing applied to the cord to a difference of 6.7% for drying.

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Table 5. Newborn coverage indicators, by survey and early breastfeeding status. The differences in coverage between those with early breastfeeding and those without was meta–analyzed for the pooled difference across surveys

Description	Survey	Among those breastfed in first hour Estimate (%)	Among those not breastfed in first hour Estimate (%)	Difference (BF – not BF) Estimate (%)	95% Confidence interval (%) Lower	Upper
Bathed after 24 h	Malawi 2014	21.6	23.1	–1.5	–12.8	9.9
	Nigeria 2013	4.9	3.2	1.6	0.3	2.9
	Bangladesh 2007	43.3	36.4	6.9	1.3	12.5
	Bangladesh 2011	61.5	52.0	9.5	4.7	14.3
	Bangladesh 2014	66.7	59.0	7.8	1.3	14.3
	Nepal 2006	12.2	10.6	1.6	–2.0	5.3
	Nepal 2011	36.2	24.8	11.3	3.9	18.8
	Timor–Leste 2009	4.6	6.3	–1.7	–4.0	0.6
	Pooled			4.0	1.1	6.9
Dried	Malawi 2014	85.9	79.2	6.7	–3.0	16.4
	Nigeria 2013*	30.3	26.7	3.6	0.1	7.1
	Bangladesh 2007	5.2	7.4	–2.2	–4.6	0.1
	Bangladesh 2011	55.0	48.9	6.2	1.3	11.1
	Bangladesh 2014	69.5	61.8	7.7	2.4	13.0
	Nepal 2006*	49.5	39.5	10.0	3.1	16.9
	Nepal 2011*	64.3	56.0	8.3	1.7	15.0
	Timor–Leste 2009*	67.6	51.5	16.1	10.0	22.1
	Pooled			6.7	2.2	11.2
New or boiled blade	Malawi 2014	96.0	95.4	0.6	–4.0	5.2
	Nigeria 2013	92.5	92.6	–0.1	–2.0	1.9
	Bangladesh 2007	82.5	82.7	–0.2	–4.2	3.8
	Bangladesh 2011	85.2	83.5	1.7	–2.0	5.5
	Bangladesh 2014	82.7	84.7	–1.9	–6.0	2.1
	Nepal 2006	82.0	76.9	5.1	–0.1	10.4
	Nepal 2011	85.7	80.2	5.5	0.1	11.0
	Timor–Leste	21.0	17.2	3.8	–0.4	8.1
	Pooled			1.3	–0.4	3.0
Nothing applied to cord	Malawi 2014	66.2	66.9	–0.7	–10.9	9.5
	Nigeria 2013	60.0	66.7	–6.7	–10.7	–2.8
	Bangladesh 2007	48.0	54.2	–6.1	–11.9	–0.4
	Bangladesh 2011	57.9	52.4	5.5	1.0	10.0
	Bangladesh 2014	49.6	52.7	–3.1	–9.9	3.6
	Nepal 2006	78.3	73.4	4.9	–0.1	9.8
	Nepal 2011	62.7	55.1	7.6	0.3	14.9
	Timor–Leste	52.3	60.2	–7.9	–13.7	–2.1
	Pooled			–0.1	–5.5	3.7
Skin to skin	Nigeria 2013	12.4	8.4	4.1	1.6	6.5
	Bangladesh 2014	25.9	25.8	0.1	–5.1	5.3
	Nepal 2011	13.1	8.7	4.4	0.5	8.4
	Pooled			3.6	1.7	5.5
Wrapped	Bangladesh 2007	1.7	2.1	–0.4	–1.6	0.8
	Bangladesh 2011	32.6	32.9	–0.3	–4.8	4.2
	Nepal 2006†	50.0	41.1	8.9	1.8	15.9
	Nepal 2011†	71.2	56.4	14.8	7.4	22.1
	Nigeria 201†	37.7	32.2	5.6	1.7	9.5
	Pooled			4.9	0.1	9.6

*Dried before delivery of placenta.
†Wrapped before delivery of placenta.

DISCUSSION

With little guidance on how to measure care for newborns and, until recently, little global attention on newborn health, few nationally representative household surveys have measured newborn care practices. In a ten year period, we identified only twelve surveys across eight countries, and several of these surveys asked about few practices. There was inconsistency across surveys in how and to whom newborn care questions were asked, which limits comparability. DHS and MICS have now offered standard questions to improve the consistency of data in coming years.

Early initiation of breastfeeding does not appear to be a high performing tracer indicator for essential newborn care, since it is poorly correlated with the all the other elements of newborn care in this analysis. Nor was there much difference in coverage of other practices when comparing babies who were breastfed within an hour and those who were not. In fact, no single practice was a good predictor of the coverage of other practices. In particular, there was very little correlation between coverage of any thermal care practices and coverage of cord care (and some had negative associations). Only drying and wrapping were highly correlated. Wrapping was not added to the DHS questionnaire because overlap between these two practices was previously seen in program surveys and thus it was deemed unnecessary to collect both [7]. Wrapping and "skin–to–skin" contact also appear to be weakly correlated in Nigeria 2013 and Nepal 2011. However, true skin–to–skin care and wrapping may be mutually exclusive events since a baby that is wrapped will not have exposed skin to place against the mother's bare skin. The correlation found in these two surveys may be explained by the fact that the question (Was the baby placed on the mother's belly/breast before delivery of the placenta?) did not specify skin–to–skin exposure, unlike how it was asked in Bangladesh 2014 or will be asked in future DHS and MICS (as shown in **Table 2**).

Indicator validation studies in Mozambique, Kenya, and Mexico have shown mothers have difficulty accurately reporting newborn care practices, though findings were inconsistent with drying, breastfeeding within an hour, and skin–to–skin contact meeting validation criteria in at least one study but not in other studies [21–24]. The weak correlations found in this study could be due to invalidity of indicators. On the other hand, newborn care practices may simply be inconsistently applied, which could also explain why correlations are weak with the exception of drying and wrapping. These past validation studies also had some design limitations. They could not include home birth observations, while this study was limited to only analyzing home births. Since validation for home births presents feasibility and ethical problems, triangulation of intervention coverage data with outcomes for babies born at home could be used to assess the plausibility of coverage levels. In addition, the validation studies did not ask all questions the same way they are asked in the new DHS and MICS questionnaires (including the question on initiation of breastfeeding) and did not examine the umbilical cord care practices now measured in DHS and MICS. While recall bias is a flaw of household surveys, most countries have no other means to assess coverage of these life–saving interventions. To have informative data on whether newborns are getting the services they need, questions about specific practices, aside from breastfeeding initiation, need to be added to surveys.

Nonetheless, surveys can mitigate bias due to mothers not witnessing certain practices, understanding terminology or what they saw being done for their baby, or remembering what was done, especially if a long time has passed since their last birth [25,26]. New DHS and MICS questions were developed and field tested to improve reporting. For example, validation research found a two–item question sequence improved mothers' reporting of skin–to–skin care, resulting in DHS and MICS adding two questions to their new questionnaires [22]. MICS6 also included a photo of a baby in the skin–to–skin position to help mothers understand the question. Mothers have also been shown to have difficulty reporting the exact timing of practices [16], so DHS and MICS limit the number of practices for which the mother is asked to give timing (breastfeeding initiation and first bathing) and simplified the need to recall precise timing by not requiring recall in minutes for practices within the first hour after birth. Instrument sterilization in facilities likely occurs outside the delivery room and many mothers who delivered in a facility report not knowing if the instrument was clean when asked [7], so DHS and MICS only ask questions on cutting the umbilical cord to mothers who delivered at home. Standard probes and follow–on questions could further improve recall and reduce use of leading questions [26,27], though not yet part of DHS or MICS interviewer manuals [28,29].

Many of the surveys reviewed in this paper only asked questions on newborn care for home births. The new DHS and MICS questionnaires are now designed to ask most questions for both facility and home births, because omitting facility births creates an information gap, especially as facility delivery rates rise;
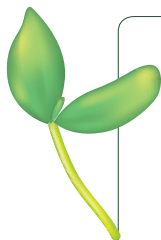
the exception is on questions on the instrument used to cut the cord [15,16]. In the future, therefore, correlations between newborn care practices for facility births can be examined. At the same time, routine data systems should be strengthened to capture newborn care practices delivered at facility and triangulate with survey data, as well as collect data on services to treat rare complications that cannot be reliably collected through national surveys.

After standardizing indicators to the extent possible, we found reported use of a clean instrument for cutting the cord among non–institutional births was high (around 80% or more) in all countries except Timor–Leste, and remained high over consecutive surveys in Bangladesh and Nepal. Coverage of dry cord care was more moderate, with a decline in Nepal from 75% in 2006 to 58% in 2011. Changing the indicator to include chlorhexidine application could not explain the decline; coverage of chlorhexidine application was low because Nepal only decided to proceed with national implementation of chlorhexidine in late 2011 [30]. As countries adopt the 2013 WHO guidelines recommending chlorhexidine application for newborns born at home in settings with high neonatal mortality [31], the appropriate indicator will be nothing *or* chlorhexidine only applied to the cord stump. Given the interest this new intervention, countries will need to know coverage. Increasing awareness of chlorhexidine may also help reporting accuracy.

Coverage levels for clean cutting and dry cord care practices in the surveys analyzed in this paper are much higher than Bhutta et al's modelled coverage estimate for the general category 'clean postnatal care practices', which was just 11% [4]. Bhutta's definition included handwashing and skin cleansing and did not include hygienic cord care, which likely explains why coverage is so different than what we found in these surveys. At the same time, countries that ask questions about hygienic cord care in national surveys may be more invested in changing these practices, so coverage may be higher than would be found others. The same may not be true for other hygienic postnatal care practices, which may be closer to Bhutta's estimate.

Early breastfeeding was generally moderate (ranging from 30% to 82%) with little change between surveys in Bangladesh and Nepal. These findings were in line with the average across all 75 countries tracked by *Countdown to 2015*, which was 50% [32]. Use of thermal care practices varied across countries, with drying, wrapping, and delayed bathing improving over time in Bangladesh and Nepal. Placing the neonate on the mother's belly or breast or on the mother's bare skin was low (10–25%). Overall, coverage estimates for thermal care practices in these surveys are substantially higher than Bhutta et al's modelled coverage estimate for 'simple thermal care' (11%). Though again, Bhutta's definition was not the same as used in this paper.

As the global community makes new commitments to the health and survival of newborns through the Sustainable Development Goals [33], countries need to know how newborns are cared for, beyond whether they are breastfed early. This study found coverage can vary greatly for different practices as well as differences across countries. There may not be a single way forward to improve the care of newborns, so country level data on multiple newborn care practices are critical. Essential newborn care may have even greater benefit for preterm babies, so having data to guide efforts to improve coverage of all practices will be important to reducing child mortality, now that prematurity is the leading cause of death for children under 5 [1]. New standards in household surveys will increase the availability of coverage estimates for these life–saving interventions for a key vulnerable population.

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<div style="writing-mode: vertical-rl">PAPERS</div>

Skilled attendant at birth and newborn survival in Sub–Saharan Africa

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Background Recent studies have shown higher neonatal mortality among births delivered by a skilled attendant at birth (SAB) compared to those who were not in sub–Saharan African countries. Deaths during the neonatal period are concentrated in the first 7 days of life, with about one third of these deaths occurring during the first day of life. We reassessed the relationship between SAB and neonatal mortality by distinguishing deaths on the first day of life from those on days 2–27.

Methods We used data on births in the past five years from recent demographic and health survey (DHS) between 2010 and 2014 in 20 countries in sub–Saharan Africa. The main categorical outcome was 1) newborns who died within the first day of birth (day 0–1), 2) newborns who died between days 2–27, and 3) newborns who survived the neonatal period. We ran generalized linear mixed model with multinomial distribution and random effect for country on pooled data. Additionally, we ran a separate model restricted to births with SAB and assessed the association of receipt of seven antenatal care (ANC) and two immediate postnatal care interventions on risk of death on days 0–1 and days 2–27. These variables were assessed as proxy of quality of antenatal and postnatal care.

Results We found no statistically significant difference in risk of death on first day of life between newborns with SAB compared to those without. However, after the first day of life, newborns delivered with SAB were 16% less likely to die within 2–27 days than those without SAB (OR = 0.84, 95% CI = 0.71–0.99). Among births with skilled attendant, those who were weighed at birth and those who were initiated early on breastfeeding were significantly less likely to die on days 0–1 (respectively OR = 0.42 95% CI = 0.29–0.62 and OR = 0.24, 95% CI 0.18–0.31) or on days 2–27 (OR = 0.60, 95% CI = 0.45–0.81 and OR = 0.59, 95% CI = 47–0.74, respectively). Newborns whose mothers received an additional ANC intervention had no improved survival chances during days 0–1 of life. However, there was significant association on days 2–27 where newborns whose mothers received an additional ANC interventions had higher survival chances (OR = 0.95, 95% CI = 0.93–0.98).

Conclusion Findings demonstrate the vulnerability of newborns immediately after birth, compounded with insufficient quality of care. Improving the quality of care around the time of birth will significantly improve survival and therefore accelerate reduction in neonatal mortality in sub–Saharan African countries. Improved approaches for measuring skilled attendant at birth are also needed.

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Global level of mortality among children under–five has been halved since 1990, with a decline from 91 deaths per 1000 live birth to 43 in 2015. A similar decline was also observed in sub–Saharan Africa, the region with the highest burden of mortality [1]. The pace of mortality decline was much slower among neonates, with sub–Sahara Africa recording one of the slowest declines of 38% over the same period, just behind Oceania where level of mortality is much lower. Subsequently, there is an increasing share of new-born deaths among all under–five deaths, reaching over a third in sub–Saharan Africa. The increasing mortality compression to the first days of life has raised calls for greater focus on newborn, with the adoption of the Every Newborn Action Plan (ENAP) in June 2014 and the subsequent publication of a Lancet Newborn Series to galvanize evidence–based programming that would accelerate reduction of newborn death toward ending preventable deaths [2]. The ENAP highlighted the strategic benefit of focusing on quality care around the time of birth by ensuring that all pregnancies have access to skilled quality care necessary for a healthy pregnancy and to protect the life of the newborn, and care for small and sick new-borns [3,4]. The WHO has defined skilled attendant at birth as "an accredited health professional — such as a midwife, doctor or nurse — who has been educated and trained to proficiency in the skills needed to manage normal (uncomplicated) pregnancies, childbirth and the immediate postnatal period, and in the identification, management and referral of complications in women and newborns" [5]. This defini-tion is currently being revised to clarify the competencies and extend to the notion of competent quali-fied maternal and newborn health care professional. [6] However, it does not address the limitation in measurement of skilled attendant at birth. In the absence of comparable data on quality skilled care, so far the world has mostly relied on the indicator of access to skilled attendant at delivery to monitor the likelihood that pregnancies receive some sort of quality of delivery care. Despite its limitation, this indi-cator has been one of the key coverage monitoring indicator in the Millennium Development Goals and more recently also adopted in the Sustainable Development Goals [7]. Skilled attendant at birth is also monitored as a core indicator in the ENAP and the Ending Preventable Maternal Mortality (EPMM) [8]. However, increasing number of studies calls for going beyond monitoring simple contact with a health system to include content and quality of interventions received [9–11]. Furthermore, assessment of the association between births reported to have been delivered with skilled attendant and chances of surviv-al beyond the neonatal period did not generate expected results, especially in sub–Saharan Africa and Asia. In a recent study that included three countries each of three regions – Asia, sub–Saharan Africa and Latin America, Singh and her colleagues showed that skilled delivery did not appear to improve the sur-vival of the newborn on the first day or week of life in the sub–Saharan African and Asian countries [12]. Possible explanations to this counter–intuitive finding highlight low quality of maternal and newborn services such that, although pregnant women come into contact with the health system to deliver, criti-cal interventions needed to save the newborn in case of complications during delivery or postnatal pe-riod are not always available [13,14]. Other explanations include selection bias and uncertainty in the measurement of skilled attendant at birth in household surveys. Most women respondents in these sur-veys are of low schooling and not able to recall the type of cadre of health worker that provided the de-livery care [15]. Regarding the selection bias, it is thought that in resource–constrained settings where access to health facility remains challenging and coverage of health facility use relatively low, women ac-cessing delivery services in health facilities are likely to be those of higher potential risk of obstetric com-plication. A substantial portion of these women arrive late in health facilities, which may also not be prop-erly equipped to promptly attend to the emergency [16–18].

In this study, we reassessed this relationship in a larger number of sub–Saharan African countries and by distinguishing deaths on the first day of life from days 2–27 using a multinomial mixed model. We con-jecture that if the selection effect is real, the positive association between SAB and mortality will be seen only during the first day of life, when newborns are particularly vulnerable. Past this period, a negative association should be observed. Regarding quality of care, we also assessed association between the re-ceipt of a series of seven antenatal care and two immediate postnatal care interventions by women and their newborns and mortality on days 0–1 and days 2–27.

DATA AND METHODS

We used data from recent Demographic and Health Surveys (DHSs), conducted in sub–Saharan Africa between 2010 and 2014, with information on child mortality collected using full birth history from wom-en aged 15–49 and selected antenatal and postnatal interventions. Data were available for 20 countries in sub–Saharan Africa. **Table 1** includes the list of the countries. DHSs are USAID–funded nationally rep-resentative household surveys carried out about every five years in low– and middle–income countries

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[19]. The survey program started in the mid–1980s and has been a major source of demographic, reproductive and health data in these countries. Data are collected using typically a two–stage cluster sampling (with some variation in some countries), with first stage represented by population census enumeration areas, and the second stage by households. All women of reproductive age (15–49 years) in each sampled household are interviewed. Data are collected on several modules, including a full birth history module that captures information on every live birth a woman respondent ever had and the survival status of these births. For children who died, information is collected on age at death. The breakdown of the age at death depends on the age range. For deaths under one month, age at death is collected in days, starting from day 0 (as day of birth). For deaths over 1 month of age but under two–years, age at death is collected in months, and for deaths over two years, age at death is collected in years. This information is used to estimate mortality among children under–five (neonatal, post–neonatal, infant, under–five mortality). Another module includes information on health care provided during pregnancy, delivery and the postpartum period for all live births in the five years preceding the survey. This module captures data on antenatal care, assistance at delivery and postnatal care. A limited number of interventions delivered during these stages is also collected from women's recall. The module allows computation of births who had a skilled attendant at birth. Skilled birth attendant is captured generally as doctor, nurse, and midwife but there are slight variations across countries with addition of special cadres considered skilled (**Table 1**). Linking this module to the full birth history module allows an analysis of the association between receipt of skilled delivery and neonatal mortality. We based the analysis on children born in the past five years preceding each survey. For the twenty countries with available data, these range from 1251 to 12 272 births for a total of 84 168 births.

Variables

The main outcome is death during the neonatal period. We created three categories: 1) newborns who died on days 0–1, 2) newborns who died between days 2 and 27, and 3) children under–five who survived the neonatal period. We initially also separated out deaths on days 2–7 but results of preliminary analysis were similar to those of deaths on days 8–27. We therefore grouped them together.

In addition to a binary variable on whether a birth was assisted by a skilled attendant at birth or not, we considered an additional main independent variable related to interventions received by the mother during antenatal care to capture quality of ANC. These interventions include urine test, blood test, blood pressure measured, iron supplementation, tetanus protection at birth, counselled on pregnancy complications, tested for HIV and received results. We created a categorical variable of number of interventions received by summing the indicator variable representing each intervention. We use this composite indicator as a proxy for quality of care received by the women during their pregnancy. For postnatal interventions, we considered two immediate postnatal interventions: whether the newborn was weighed at birth and whether the newborn was initiated early on breastfeeding. The latter was captured by asking the mother whether the newborn was breastfed within one hour following birth. We could not consider other available postnatal indicators in the analysis due to possible selection bias that would be introduced, given newborns who died immediately during the first days of life would not have the same exposure time to the chance of receiving these interventions.

We considered as control variables, socio–economic and demographic variables with known effects on mortality. These included residence (urban, rural), wealth quintile (poorest, poorer, middle, richer, richest), marital status (single, married, other), parity (1, 2–4, 5 or more), mother's age at birth (15–19, 20–29, 30–39, 40–49 years), and mother's education level (no schooling, primary, secondary or higher).

Analysis

We first described the coverage of skilled attendant at birth in the twenty countries. For each country, we computed and compared neonatal mortality rate separately for births with a skilled birth attendant and those without. We computed these rates on the three years preceding each survey using a life table approach [20]. To compare the rates, we computed 95% confidence intervals using Jackknife approach [21]. We then pooled all country data and fit a generalized linear mixed model with multinomial distribution and random effect for country. We used the third category of the outcome variables (children under–five who survived the neonatal period) as the reference category. We estimated two models. First, we fit a model of mortality outcome on skilled attendance at birth, adjusting for the control variables described above. Second, we fit a model of mortality outcome on number of ANC interventions received, and the immediate postnatal variables controlling for socio–demographic variables. The latter model included

data from 18 countries and was restricted to only births delivered with skilled health personnel to assess the effect of quality of care on newborn death. The mortality computation analyses were carried out in STATA version 13 while the regression models were implemented in SAS.

RESULTS

Table 1 and **Figure 1** show levels of coverage of skilled attendant at birth (SAB) by country. Coverage ranged from 29% in Niger to 93% in Congo with a median of 62%. Table 1 also shows the five–year neonatal mortality rate by country, ranging from 22 deaths per 1000 live births in Congo to 39 deaths per 1000 live births in Sierra Leone. There is a marginally significant inverse relationship between SAB and neonatal mortality: (r=−0.42, P<0.0619). While Congo shows the highest coverage of SAB and lowest neonatal mortality, the country with lowest coverage of SAB (Niger) does not have the highest neonatal mortality. **Figure 2** presents the neonatal mortality rate by SAB along with the 95% confidence intervals. The general picture across countries suggests no significant survival advantage during the neonatal period among births with SAB and those without. Based on the confidence intervals, there is no statistically significant
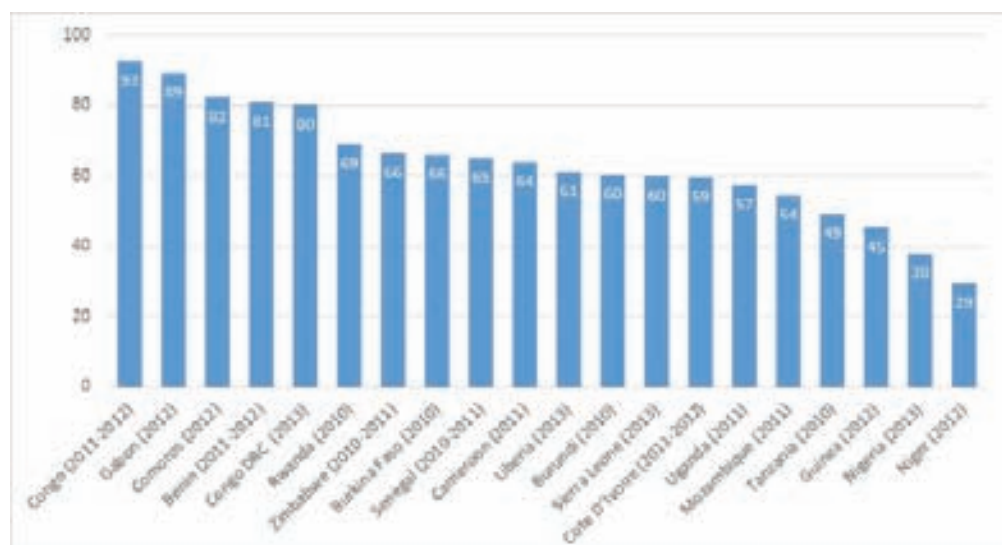
Figure 1. Percent of live birth in the five years preceding the survey with skilled attendant at birth by country, Demographic and Health Survey (DHS, 2010–2014). Survey years are included in the parenthesis.
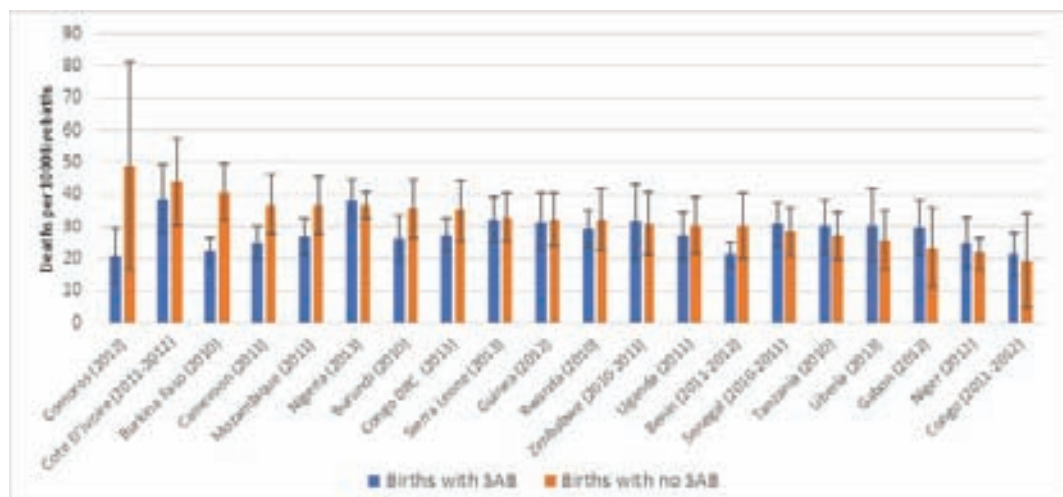
Figure 2. Neonatal mortality rate and 95% confidence intervals according to whether the birth had a skilled attendant at birth (SAB) or not by country.

Table 1. Percentage of births with skilled health personnel and neonatal mortality rate by country

Country	Survey year	Percentage of births with skilled health personnel	Neonatal mortality (five year preceding the survey)*	Number of live births in the five years preceding the survey	Definition of skilled attendant at birth
Benin	2011–2012	80.9	23	5147	Doctor, nurse/midwife
Burkina Faso	2010	65.9	28	5790	Doctor, nurse/midwife, auxiliary midwife
Burundi	2010	60.3	31	3007	Doctor, nurse/midwife
Cameroon	2011	63.6	31	4496	Doctor, nurse/midwife
Comoros	2012	82.2	24	1251	Doctor, nurse/midwife
Congo	2011–2012	92.5	22	3625	Doctor, nurse/midwife, Assistant
Cote D'Ivoire	2011–2012	59.4	38	3041	Doctor, nurse/midwife
Democratic Republic of the Congo	2013	80.1	28	7209	Doctor, nurse/midwife
Gabon	2012	89.3	26	2443	Doctor, nurse/midwife
Guinea	2012	45.3	33	2763	Doctor, nurse/midwife, auxiliary midwife
Liberia	2013	61.1	26	2984	Doctor, nurse/midwife
Mozambique	2011	54.3	30	4543	Doctor, nurse/midwife
Niger	2012	29.3	24	4738	Doctor, nurse/midwife
Nigeria	2013	38.1	37	12272	Doctor, nurse/midwife
Rwanda	2010	69.0	27	3119	Doctor, nurse/midwife
Senegal	2010–2011	65.1	29	4771	Doctor, nurse/midwife
Sierra Leone	2013	59.7	39	4652	Doctor, nurse/midwife
Uganda	2011	57.4	27	2949	Doctor, nurse/midwife
United Republic of Tanzania	2010	48.9	26	3010	Doctor/assistant medical officer, nurse/midwife, clinical officer, assistant clinical officer
Zimbabwe	2010–2011	66.2	31	2358	Doctor, nurse/midwife
MEDIAN		62.3			
Correlation between SAB and NMR		**−0.42 (*P* < 0.0619)**			

*From STATCompiler, StatCompiler.com, accessed on February 2, 2017.

difference in neonatal mortality rate among births with SAB compared to those without, except in Burkina Faso where births with SAB have significantly lower neonatal mortality than those without.

Table 2 presents results from the multinomial mixed model regression. Births who survived beyond the neonatal period are used as reference category. Furthermore, the reference category corresponding to each categorical variable included in the model is shown in parenthesis beside the name of the variable in the first column. Column 2 shows the age at death, distinguishing deaths on days 0–1 and deaths on days 2–27, and column 3 shows the response category of the independent variable included in the model. Response categories with significant results are bolded. Adjusting for covariates in the model, there is no statistically significant difference in the odds of death on days 0–1 between births with SAB and births without. However, births with SAB who survived after the first day showed a statistically significant 16% lower risk of death on the period 0–27 days compared to births without SAB (OR = 0.84, 95% CI = 0709–0.996). Several demographic covariates remained statistically significant in the model. These include parity, mother's age at birth of the child, and current marital status. With regard to parity, there is no differential risk of death for first birth compared to births of parity 5 plus whether on days 0–1 or days 2–27. However, births of parity 2–4 have significantly 25% lower odds of death on the days 2–27 compared to births of parity 5 plus. Compared to births to women aged 20–29, births to older women have higher odds of death on either days 0–1 or days 2–27. Births to women aged 40 or more have respectively 72% and 62% higher odds of death on days 0–1 and days 2–27 compared to births to women aged 20–29. For births to women 30–39, the differential risk is observed only for births on days 0–1, with a 25% increased odds of death. Births to single women have 52% higher odds of death compared to births to married women. Other characteristics such as education level, residence or wealth quintile showed no significant differential risk of death on days 0–1 or days 2–27.

In Table 3, we present results from the multinomial mixed model regression, restricted to only births with SAB and assessing the effect of co–coverage of interventions during ANC and immediate postnatal interventions, adjusting for the same socio–demographic characteristics. Statistically significant variables are shown in bold. Adjusting for the socio–demographic variables included in the model and immediate postnatal interventions, there is a strong and negative significant association between the number of ANC

Table 2. Adjusted odds ratios of death on days 0–1 or days 2–27 compared to surviving over the neonatal period among births with SAB compared to births without SAB)*

Variable (reference category)	Age at death	Category	Odds Ratio	95% confidence interval		P
Skilled attendant at birth (No.)	Day 0–1	Yes	1.17	0.934	1.465	0.173
	Day 2–27	**Yes**	**0.84**	**0.709**	**0.996**	**0.045**
Parity (5 plus)	Day 0–1	1	1.35	0.919	1.984	0.127
	Day 2–27	1	1.03	0.708	1.506	0.870
	Day 0–1	2–4	0.84	0.678	1.051	0.129
	Day 2–27	**2–4**	**0.75**	**0.607**	**0.931**	**0.009**
Mother's age at birth (20–29)	Day 0–1	15–19	0.91	0.757	1.106	0.358
	Day 2–27	15–19	1.15	0.879	1.517	0.301
	Day 0–1	**30–39**	**1.25**	**1.052**	**1.488**	**0.011**
	Day 2–27	30–39	1.14	0.937	1.376	0.194
	Day 0–1	**≥40**	**1.72**	**1.349**	**2.187**	**<0.0001**
	Day 2–27	**≥40**	**1.62**	**1.247**	**2.099**	**<0.0001**
Current marital status (Married)	Day 0–1	Other	1.01	0.871	1.172	0.896
	Day 2–27	Other	1.15	0.939	1.414	0.175
	Day 0–1	Single	1.08	0.811	1.427	0.611
	Day 2–27	**Single**	**1.52**	**1.218**	**1.906**	**<0.0001**
Education level (No education)	Day 0–1	Primary	1.04	0.896	1.215	0.585
	Day 2–27	Primary	1.04	0.92	1.171	0.545
	Day 0–1	Secondary or higher	0.92	0.704	1.202	0.542
	Day 2–27	Secondary or higher	0.84	0.649	1.089	0.189
Residence (Rural)	Day 0–1	Urban	1.01	0.837	1.218	0.920
	Day 2–27	Urban	1.14	0.92	1.401	0.237
Wealth quintile (Poorest)	Day 0–1	Poorer	1.03	0.852	1.239	0.776
	Day 2–27	Poorer	1.05	0.893	1.241	0.542
	Day 0–1	Middle	1.04	0.911	1.180	0.585
	Day 2–27	Middle	1.00	0.805	1.234	0.973
	Day 0–1	Richer	1.04	0.877	1.224	0.678
	Day 2–27	Richer	0.94	0.755	1.173	0.590
	Day 0-1	Richest	1.05	0.828	1.323	0.705
	Day 2-27	Richest	0.91	0.619	1.328	0.614

SAB – skilled attendant at birth

*Analysis based on generalized linear mixed model; pooled DHS 2010-2014 from 20 countries in Africa.

interventions received and the odds of death on days 2–27. The odds of death on days 2–27 are reduced by 5% for each additional ANC intervention received. However, this advantage was not observed on days 0–1 and in fact there appeared to be a marginal positive association between number of ANC interventions and risk of death. Regarding immediate postnatal interventions, newborns weighed at birth or those initiated early on breastfeeding were significantly less likely to die either on days 0–1 or days 2–27. Newborns weighed at birth were 58% less like die on days 0–1 and 40% less likely to die on days 2–27. Similarly, newborns initiated early on breastfeeding were respectively 76% and 41% less likely to die on days 0–1 and days 2–27. The demographic characteristics such as parity, mother's age and marital status remained significant and in the similar direction as described for the model in **Table 2**. However, urban–rural residence, education level and wealth quintile became statistically significant in this model in somewhat unexpected direction.

DISCUSSION

Access to skilled attendant at birth during antenatal care and delivery is promoted as a key strategy for improving maternal and newborn care in low and middle–income countries. The importance of skilled personnel at the time of birth is widely acknowledged, such that the proportion of births attended by skilled health personnel has been adopted as a key coverage monitoring indicator for the Sustainable Development Goal 3.1. However, we showed in this study that the survival benefits expected for newborns delivered with skilled health personnel are not being observed in sub–Saharan Africa. We demonstrated in the analysis that there is no survival benefit on days 0–1 for newborns, whether they are delivered by

Table 3. Adjusted odds ratios of death on days 0–1 or days 2–27 compared to surviving over the neonatal period by number of ANC interventions received by mother and immediate postnatal interventions received by newborn (among births with SAB)*

Independent variable	Age at death	Category	Odds ratio	95% confidence interval		P–value
Number of seven ANC interventions received by mother	**Day 0–1**	**Continuous**	**1.02**	**1.000**	**1.044**	**0.0545**
	Day 2–27	**Continuous**	**0.95**	**0.927**	**0.979**	**0.0005**
Newborn weighed at birth (No.)	**Day 0–1**	**Yes**	**0.42**	**0.292**	**0.615**	**<.0001**
	Day 2–27	**Yes**	**0.60**	**0.450**	**0.809**	**0.0007**
Newborn initiated early on breastfeeding (No)	**Day 0–1**	**Yes**	**0.24**	**0.184**	**0.310**	**<.0001**
	Day 2–27	**Yes**	**0.59**	**0.473**	**0.744**	**<.0001**
Parity (5 plus)	**Day 0–1**	**1**	**1.54**	**1.030**	**2.307**	**0.0356**
	Day 2–27	1	1.19	0.817	1.728	0.3668
	Day 0–1	2–4	0.91	0.723	1.151	0.4372
	Day 2–27	**2–4**	**0.80**	**0.645**	**1.002**	**0.0518**
Mother's age at birth (20-29)	Day 0–1	15–19	0.86	0.702	1.043	0.1225
	Day 2–27	15–19	1.04	0.790	1.361	0.7941
	Day 0–1	**30–39**	**1.27**	**1.056**	**1.519**	**0.011**
	Day 2–27	30–39	1.16	0.941	1.432	0.1633
	Day 0–1	**≥40**	**1.80**	**1.376**	**2.364**	**<.0001**
	Day 2–27	**≥40**	**1.60**	**1.192**	**2.142**	**0.0017**
Current marital status (Married)	Day 0–1	Other	1.02	0.874	1.179	0.8458
	Day 2–27	Other	1.09	0.898	1.318	0.3867
	Day 0–1	Single	1.05	0.799	1.389	0.7119
	Day 2–27	**Single**	**1.47**	**1.162**	**1.861**	**0.0013**
Education level (No education)	**Day 0–1**	**Primary**	**1.23**	**1.064**	**1.417**	**0.0051**
	Day 2–27	**Primary**	**1.14**	**0.990**	**1.304**	**0.0695**
	Day 0–1	Secondary or higher	1.17	0.883	1.549	0.2734
	Day 2–27	Secondary or higher	0.97	0.770	1.215	0.7736
Residence (Rural)	Day 0–1	Urban	1.13	0.917	1.401	0.2456
	Day 2–27	**Urban**	**1.27**	**1.030**	**1.559**	**0.0254**
Wealth quintile (Poorest)	Day 0–1	Poorer	1.14	0.937	1.378	0.1945
	Day 2–27	Poorer	1.11	0.944	1.304	0.2079
	Day 0–1	**Middle**	**1.27**	**1.096**	**1.463**	**0.0014**
	Day 2–27	Middle	1.08	0.888	1.323	0.4300
	Day 0–1	**Richer**	**1.42**	**1.155**	**1.736**	**0.0008**
	Day 2–27	Richer	1.07	0.850	1.338	0.5777
	Day 0–1	**Richest**	**1.68**	**1.267**	**2.225**	**0.0003**
	Day 2–27	Richest	1.08	0.767	1.527	0.6531

ANC – antenatal care, SAB – skilled attendant at birth
Analysis based on generalized linear mixed model; pooled DHS 2010–2014 data from 18 countries in Africa.

a skilled birth attendant or not. Only when they survive day 1 does such benefit occur. These results are consistent with previous studies and call once again for greater attention to the fragility of care around the time around of delivery [3,4,11]. The results suggest that skilled birth attendants, and most health facilities, are not yet equipped enough to save newborns at highest risk of death immediately after birth. These results were further corroborated by assessing effects of quality of care immediately after birth on the risk of death among births with skilled attendant. Among these births, simple interventions such as being weighed at birth or being initiated on breastfeeding early showed strong and significant benefits for survival chances during the neonatal period. It may be that these interventions are also good proxy for quality of care during the immediate postnatal period. Using the number of antenatal care interventions that the mother received did not show survival benefits for births attended by skilled personnel on days 0–1, but only on days 2–27, reinforcing the finding that interventions delivered immediately after birth are most critical for the survival of the newborn during the immediate periods following birth.

In **Table 4**, we estimated, based on annual births, stillbirth and number of skilled health professionals, the number of deliveries per skilled health professional given current coverage, and for 100% coverage. The estimated number of deliveries per skilled health professional ranges from 8 in Nigeria to 120 in Guinea. While these are average estimates and do not account for highly unequal distribution of skilled health professional within countries or that some health professional may not conduct deliveries at all, and there is highly unequal distribution of deliveries for each provider, their level is not extremely high

as to overwhelm the health system. Lack of significantly improved survival among those who access these professionals during the immediate postnatal period may suggest that the system is not sufficiently equipped and strong enough to deal with high–risk obstetric conditions and/or a substantial portion of these health personnel is not skilled enough to prevent such risks from leading to death. It also suggests highly inequitable distribution of SAB or facilities with lower access in higher risk populations. Even with 100% coverage of skilled delivery, a country like Nigeria will see only an average of 20 deliveries per skilled health personnel, and in most countries skilled health personnel will perform on average fewer than 100 deliveries per year.

In such conditions, it is not entirely inappropriate to question whether it still makes sense to continue to advocate for increased skilled delivery when this strategy is not producing the expected survival advantage in resource constrained countries. The answer from our study would be yes, because, at least beyond the first two days of life, there is significant survival advantage for newborns delivered with skilled birth attendants. Nevertheless, the question underscores the tremendous missed opportunities for the health system when women are encouraged to deliver in health facilities with skilled attendant, yet do not receive needed quality of care when they show up. The lack of survival advantage during the first days of life for the newborn, even when delivery occur with skilled personnel or in health facility can reinforce barriers to facility use.

Our results raise three main implications, which are also generally raised to explain the lack of significant improvement in survival of newborns delivered with skilled attendants compared those without. First is the need for improving access to equitable high–quality maternal and delivery care in African countries. Many studies have demonstrated the low level of quality of care, including low access to basic and emergency obstetric services. Nesbitt and colleagues showed a quality gap, defined as the difference between the crude coverage of SAB and the coverage of SAB with high quality of care, as large as 50 percentage points in health facilities in several districts in Ghana. Marchant raised the concern that contacts with the health system are not used sufficiently to deliver life–saving, timely interventions. While these studies have either assessed readiness of health facilities or delivery of interventions according to international or WHO–recommended standards, another important knowledge gap remains, namely an accurate assessment of care provision decision–making process based on obstetric risk to the woman or her newborn in resource–constrained settings. In an environment where there are not enough equipment, drugs or human resources, how health professionals decide on who should get what interventions and who should not, is not always factored in the measure of quality of care. It is clear that if, given such shortages, only a few patients can receive an intervention, some triage process will need to be in place based on obstetric risk. Under such circumstances, measures of quality of care based on optimal international standards applicable to every woman regardless of risk, or a sum of required interventions that every pregnant woman must receive will always yield low quality of care. The understanding of care provision and triage decision–making process that health care workers are forced to make when faced with a shortage of essential equipment and drugs will allow an appropriate and contextualized remedy on how countries should adapt international standards to their specific resource constrained contexts. For example, to tackle the shortage of qualified health professionals, countries have resorted to task–shifting, with increasing reliance on lower level health professionals, including in some cases community health workers. However, it is essential that countries which adopt such strategies ensure that it is accompanied with the appropriate education, skill upgrade training, and necessary equipment within a mentorship and supportive environment. Another critical aspect is the extent to which quality of care is equitable across facilities, regions and population groups. Equitable access to quality care is closely linked to population level effective coverage, a proximal determinant of survival impact. In a context of equitable access, results shown in **Table 4** would not imply overburdened delivery system, in terms of human resources.

Second, while there is a standard definition of skilled health personnel, its application at country level and its measurement remain a challenge at country level [5]. While WHO and UNICEF are rallying the midwifery and newborn communities to revise the current definition, its applicability at country level will always face contextual challenges, where most of qualified health personnel do not work where the need for them is highest. Rural, poor and difficult access areas will remain disadvantaged since no doctors or qualified personnel will opt to go there without substantial benefits. Countries will therefore continue to use task shifting strategy to address accessibility issues in poor areas. Under such conditions, expanding the training of all those involved in maternal and newborn care to raise their skills, and equipping facilities for basic and emergency obstetric and newborn care would be a reasonable strategy. Furthermore, the measurement of skilled birth attendant through household surveys is also challenged with mis-

Table 4. Estimated average annual deliveries per skilled health professional by country

Country	Total popula-tion 2015 (in 1000s)ᵃ	Births in 2015 (in 1000s)*	Number of stillbirths in 2015†	Skilled health professionals density (per 10 000 population)‡	Estimated No. of skilled health professionals	Percentage of births with skilled health professional	Number of annual deliveries per skilled health professional§	Number of annual deliveries per skilled health professional if 100% coverage
Benin	10 880	388	11 700	8.3	9030	80.9	36	44
Burkina Faso	18 106	717	14 900	6.1	11 044	65.9	44	66
Burundi	11 179	488	12 700	–	–	60.3	–	–
Cameroon	23 344	847	16 400	5.2	12 139	63.6	45	71
Comoros	788	26	800	–	–	82.2	–	–
Congo	4620	167	2500	9.2	4251	92.5	37	40
Cote d'Ivoire	22 702	838	22 800	6.3	14 302	59.4	36	60
Democratic Republic of the Congo	77 267	3217		–	–	80.1	–	–
Gabon	1725	51	700	–	–	89.3	–	–
Guinea	12 609	460	9900	1.4	1765	45.3	120	266
Liberia	4503	156	3300	2.9	1306	61.1	75	122
Mozambique	27 978	1087	20 700	4.5	12 590	54.3	48	88
Niger	19 899	983	36 200	1.6	3184	29.3	94	320
Nigeria	182 202	7133	313 700	20.1		38.1	8	20
Rwanda	11 610	363	5900	7.5	8707	69.0	29	42
Senegal	15 129	567	14 500	4.8	7262	65.1	52	80
Sierra Leone	6453	229	5400	1.9	1226	59.7	114	191
Uganda	39 032	1665	34 200	14.2	55 426	57.4	18	31
United Republic of Tanzania	53 470	2064	47 100	4.7	25 131	48.9	41	84
Zimbabwe	15 603	539		14.2	22 156	66.2	16	25

*Source: United Nations, Department of Economic and Social Affairs, Population Division [22].
†Source: Lawn et al [23].
‡Source: WHO [24].
§Assumed same coverage level of skilled health personnel for stillbirths.

classification and inaccuracy. Low literacy mothers delivering in facilities do not always know the cadre of health professional in charge of their delivery [25,26]. In addition, categories of cadres of health personnel used in survey instruments such as those in DHS or Multiple Indicator Cluster Surveys (MICS) are not consistent across time and countries. Furthermore, the type of cadres that are included as skilled varies largely within and between countries. This creates difficulties in assessing accurately, not only the coverage levels of SAB but its trends. A growing number of studies are now researching measurement approaches based on linking of household surveys to health facilities [27,28]. While findings from these studies will be very valuable, an immediate step to take is for large survey programs such as the DHS and the Multiple Indicator Cluster Surveys (MICS) to standardize their instruments across surveys and time to allow comparability of results over time. While measurement issues with skilled attendant at birth could have affected our findings above, it is important to note that the large majority of births reported being delivered with skilled personnel occurred in health facilities in these countries. The findings therefore stand for births occurring in health facilities and highlight the tremendous missed opportunities and insufficient quality of care that substantial number of pregnant women face in countries included in this study.

Finally, there has been a suggestion that lack of improved outcomes at facility levels could be due to higher obstetric risk pregnancies rushing to the facility, which increases the risk profile of births with skilled attendants vs those without [16–18]. While this may be happening, it also suggests that drastic measures to improve access to timely antenatal care, counselling on institutional delivery or access to skilled delivery and attention to quality of care, including respectful maternal care, are to be prioritized. Implementation of quality pre–delivery maternity homes may be a solution to delayed access in some contexts [29].

Ending preventable newborn death while relying on current health systems in sub–Saharan African countries will require not only improvement in access to skilled delivery but also drastic measures to ensure effective coverage by improving availability of equipment and essential medicine, and equitable distribution of health personnel that is ready to deliver lifesaving interventions especially at time around delivery.

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The importance of skin–to–skin contact for early initiation of breastfeeding in Nigeria and Bangladesh

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Background Skin–to–skin contact (SSC) between mother and newborn offers numerous protective effects, however it is an intervention that has been under–utilized. Our objectives are to understand which newborns in Bangladesh and Nigeria receive SSC and whether SSC is associated with the early initiation of breastfeeding.

Methods Demographic and Health Survey (DHS) data were used to study the characteristics of newborns receiving SSC for non–facility births in Nigeria (DHS 2013) and for both facility and non–facility births in Bangladesh (DHS 2014). Multivariable logistic regression was used to study the association between SSC and early initiation of breastfeeding after controlling for key socio–demographic, maternal and newborn–related factors.

Results Only 10% of newborns in Nigeria and 26% of newborns in Bangladesh received SSC. In the regression models, SSC was significantly associated with the early initiation of breastfeeding in both countries (OR = 1.42, 95% CI 1.15–1.76 for Nigeria; OR = 1.27, 95% CI 1.04–1.55, for Bangladesh). Findings from the regression analysis for Bangladesh revealed that newborns born by Cesarean section had a 67% lower odds of early initiation of breastfeeding than those born by normal delivery (OR = 0.33, 95% CI 0.26–0.43). Also in Bangladesh newborns born in a health facility had a 30% lower odds of early initiation of breastfeeding than those born in non–facility environments (OR = 0.70, 95% CI 0.53–0.92). Early initiation of breastfeeding was significantly associated with parity, urban residence and wealth in Nigeria. Geographic area was significant in the regression analyses for both Bangladesh and Nigeria.

Conclusions Coverage of SSC is very low in the two countries, despite its benefits for newborns without complications. SSC has the potential to save newborn lives. There is a need to prioritize training of health providers on the implementation of essential newborn care including SSC. Community engagement is also needed to ensure that all women and their families regardless of residence, socio–economic status, place or type of delivery, understand the benefits of SSC and early initiation of breastfeeding.

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Globally there were an estimated 5.9 million deaths to children under–five in the year 2015, and 45% of these deaths occurred during the neonatal period, the first month of life [1]. While there have been substantial reductions in under–five mortality, reductions in neonatal mortality have been less pronounced. From 1990 to 2015 under–five mortality fell by 52%

compared to 42% for neonatal mortality [1]. The main causes of under–five mortality are now prematurity, pneumonia; and intrapartum–related conditions including birth asphyxia [2]. Notably two of the top three main causes of death occur either exclusively in the neonatal period (birth asphyxia) or mostly in the neonatal period (prematurity), while pneumonia is a cause of death for both neonates and children 1–59 months. The global health community has provided specific recommendations on essential newborn care (ENC), which refers to care provided to the newborn within the first moments to days of life [3]. Components of ENC include thermal care, early and exclusive breastfeeding, appropriate cord care and monitoring/early treatment for low birth weight or sick newborns. ENC is intended to enable countries to protect newborns through the implementation of simple, yet, life–saving interventions.

The ENC interventions focused on thermal care are intended to ensure that newborns do not develop hypothermia (state of being too cold) or hyperthermia (state of being too hot). Newborns regulate temperature less effectively and lose heat more easily compared to adults. These issues are intensified for low birth weight and premature newborns [4]. Interventions for thermal care include immediate drying, delayed bathing, head covering and skin–to–skin contact (SSC), which is the placement of a naked newborn baby prone on the mother's bare chest soon after birth [5]. The mother and baby may be covered loosely with a blanket or cloth, preferable pre–warmed [6]. The newborn baby should remain in that position until the end of the first successful breastfeeding [5,7]. In addition to providing warmth, SSC also has numerous other benefits including improved attachment between mother and newborn [8–10] and the reduction of infant stress [5,11,12]. A Cochrane Review of randomized trials including mother–baby dyads, found that SSC at birth was associated with breastfeeding at one to four months post–birth with a risk ratio of 1.25. A total of 13 trials, composing of 702 mother–baby dyads, were included in the review for the breastfeeding outcomes [5]. Despite the benefits and the simplicity of SSC as a natural intervention, over time it became common practice to separate newborns from their mothers after delivery often due to routine procedures [5,13–5]. In 2012, the American Academy of Pediatrics stated that many maternal and newborn assessments can be done during SSC or can be delayed until after the critical SSC period, so long as the mother and newborn do not have any complications [16].

There is an increased focus on newborn health interventions among the global health community and recently some large–scale household surveys have included measures of such interventions. The use of population–based data are important, as it can provide some indication of how well a country is implementing SSC in real–life settings. Data on SSC are only currently available from a few household surveys, most recently the Nigeria Demographic and Health Survey (DHS) 2013 [17] and the Bangladesh DHS 2014 [18]. These two countries together accounted for 12% of the world's neonatal deaths [1].

The first objective of this analysis is to assess the level of practice of SSC in Nigeria and Bangladesh and to examine the characteristics of newborns who are receiving SSC. Understanding SSC by key factors is essential in efforts to improve coverage of this intervention. The second objective is to determine whether SSC is associated with the early initiation of breastfeeding, defined as breastfeeding within the first hour of life. Early initiation of breastfeeding is an important outcome to study for several reasons. First milk or colostrum is rich in protective factors including antibodies and vitamin A, and early breastfeeding is a pivotal step towards longer–term and exclusive breastfeeding [19]. Trials in Nepal and Ghana have found that early initiation of breastfeeding could prevent 19% and 22%, respectively, of neonatal deaths [20,21].

METHODS

Data sources

We used data from the 2013 Nigeria DHS and the 2014 Bangladesh DHS. The DHS are a source of nationally representative data for monitoring socio–economic and health indicators at the population level. In sampled households women age 15–49 are eligible to participate, but in some countries, such as Bangladesh, only ever–married women 15–49 are eligible to participate. The sample is based on a stratified two–stage cluster design. The first stage is the sample enumeration area (SEA), and the second stage is a list of households from each SEA. The samples are representative at the national, urban/rural residence and regional levels. For both Nigeria and Bangladesh we restricted our sample to women with a live birth. For Nigeria the question on SSC was asked of the most recent birth in the past five years for non–facility births only. For Bangladesh the question on SSC was asked of the most recent birth in the past three years for both facility and non–facility births. (The specific questions are described in the section on the key

independent variable.) The sample sizes were 11 966 mother–newborn pairs in Nigeria and 4444 mother–newborn pairs in Bangladesh.

Outcome variable

The dependent variable was early initiation of breastfeeding, defined as breastfeeding within one hour of birth. The question was worded the same in both Bangladesh and Nigeria: *How long after birth did you first put (NAME) to the breast?*

The variable was coded as "0" if more than 1 hour and "1" if one hour or less.

Key independent variable

The key independent variable was a dichotomous indicator of SSC for the most recent birth in the past three (Bangladesh) or five (Nigeria) years. The questions were slightly different between the two surveys as shown below.

Nigeria (non–facility births only): *Was (Name) placed on your belly/breast before delivery of the placenta?*

Bangladesh (facility and non–facility births): *After the birth was (Name) put directly on the bare skin of your chest?*

Another difference is that in Bangladesh the interviewers were trained to show the respondent a picture of the SSC position.

Control variables

Several maternal health variables were studied including mother's age in years by the following age groups: 15–19, 20–24, 25–34, 35+; education (none, primary, secondary or higher); current marital status (married, not married) and parity (1, 2–3, 4+). The analysis included two socio–economic variables – urban residence and wealth quintile and a demographic variable–subnational region of residence (which were zones for Nigeria and divisions for Bangladesh). Several delivery–rated factors were studied including Cesarean delivery (yes/no: Bangladesh only); facility delivery (yes/no Bangladesh only; facility vs non–facility) and type of delivery attendant [skilled birth attendant (SBA) vs unskilled birth attendant]. SBA was defined as a doctor, nurse or midwife in accordance with the global definition. We included mother's perceptions of her baby's birthweight (small, average, large, large) to understand any differentials in SSC by perceived size of the baby.

Analysis

The analysis was carried out separately for each country. Bivariate analyses (using Pearson χ^2 test) compared several control variables for mothers reporting SSC immediately after birth to those who did not. In multivariate logistic regressions, early breastfeeding was regressed on SSC, controlling for all of the maternal and infant–related variables mentioned in the section above.

RESULTS

Table 1 shows column percentages of SSC by key characteristics of the mother and newborn in Nigeria. Only about 10% of mothers (1217/12 265) reported SSC, and there was little difference between mothers whose newborns received SSC and mothers whose newborns did not receive SSC. However, there was one significant difference. Newborns who were perceived to be large were significantly more likely to experience SSC than smaller newborns. About 55% of the newborns who received SSC were perceived to be large, compared to 29% and 16% for those perceived to be average and small, respectively.

Table 2 shows column percentages of SSC by key characteristics for the Bangladesh sample. Overall, about 26% of mothers (1210/4586) reported SSC with their newborn, and once again there was little difference between mothers whose newborns received SSC vs those that did not. The only significant finding was that newborns of parity 2–3 were significantly more likely to have experienced SSC with their mothers compared to newborns of parity one and higher parity. Of the newborns receiving SSC 50% were of parity 2–3 compared to 39% for newborns of parity one and 11% for newborns of parity 4 and higher. This finding, however was only significant at $P<0.10$.

Table 1. Skin-to-skin contact by key characteristics in Nigeria: Last non–facility birth in past five years (survey–weighted column percentages and counts)

	Skin–to–skin contact						P
	Yes		No		Total		
	10%	(n = 1217)	90%	(n = 11 048)	100.0%	(N = 12 265)	
Mother's age:	%	n	%	n	%	n	
15–19	7.9	96	7.7	850	7.7	946	
20–24	20.3	248	20.9	2305	20.8	2551	
25–34	45.2	551	44.9	4964	45.0	5515	
35–49	26.6	323	26.5	2929	26.5	3249	
Parity:							
1	13.8	168	14.6	1616	14.6	1784	
2–3	26.4	321	29.2	3223	28.9	3545	
4+	59.8	728	56.2	6204	56.5	6932	
Mother's education:							
None	70.3	856	68.2	7538	68.5	8394	
Primary	17.8	217	17.0	1877	17.1	2093	
Secondary+	11.8	144	14.8	1633	14.5	1774	
Zone:							
North Central	16.3	198	11.1	1227	11.6	1425	
North East	33.8	412	20.4	2253	21.7	2665	
North West	42.9	523	52.6	5809	51.6	6332	
South East	1.2	14	2.7	297	2.5	312	
South South	4.1	50	7.3	806	7.0	856	
South West	1.7	21	5.9	651	5.5	672	
Residence:							
Urban	18.7	228	20.4	2263	20.3	2486	
Rural	81.3	990	79.6	8785	79.7	9775	
Wealth:							
Poorest	38.6	470	34.8	3843	35.2	4313	
Second	27.2	331	29.8	3294	29.6	3624	
Middle	18.2	221	18.6	2057	18.6	2279	
Fourth	11.5	140	11.8	1300	11.7	1438	
Richest	4.6	56	5.0	553	4.9	606	
Estimated size at birth:							
Small	16.0	193	18.0	1973	17.8	2167	
Average	29.4	355	42.2	4630	40.9	4985	
Large	54.7	662	39.9	4378	41.3	5040	<0.001
Attendant at delivery:							
Doctor/midwife/Nurse	5.5	67	3.8	417	4.0	484	
Unskilled provider/friend/ family member/other	94.5	1141	96.2	10 588	96.0	11 729	

Table 3 shows results from regression analyses of early breastfeeding on SSC, controlling for key characteristics of mothers and newborns. In both Nigeria and Bangladesh, SSC was associated with significantly increased odds of early breastfeeding, controlling for all other variables in the models. The odds of early breastfeeding was 42% for newborns receiving SSC in Nigeria and 27% for newborns receiving SSC in Bangladesh (odds ratio (OR) = 1.42, 95% confidence interval (CI) 1.15–1.76; OR = 1.27, 95% CI 1.04–1.55, respectively). Also, in Nigeria several maternal demographic variables were associated with increased odds of early breastfeeding. Newborns of parity 2 or 3 had a 23% increased odds of SSC than newborns of parity 1 (OR = 1.23, 95% CI 1.02–1.50). Compared to North Central, the referent region, the odds of early breastfeeding were significantly lower for newborns in North West, South East and Southwest. Newborns from wealthier households were significantly more likely to experience early breastfeeding than newborns from the very poorest households. The odds ranged from 30% to 59% depending on the specific wealth quintile.

The results for Bangladesh indicated that Cesarean delivery was associated with a 67% lower odds of early breastfeeding (OR = 0.33, 95% CI 0.26–0.43), and facility delivery was associated with a 30% lower

odds of early breastfeeding (OR = 0.70, 95% CI 0.53–0.92). There were also two significant effects for division. Compared to the referent division, Barisal, residence in Rangpur was associated with a 50% higher odds of early breastfeeding (OR = 1.50, 95% CI 1.03–2.17) and in Sylhet with a 42% higher odds of early breastfeeding (OR = 1.42, 95% CI 1.02–1.96).

Table 2. Skin–to–skin contact by key characteristics in Bangladesh: last birth in past three years (survey–weighted column percentages and counts)

	SKIN–TO–SKIN CONTACT						P
	Yes		No		Total		
	26%	(n = 1210)	84%	(n = 3376)	100.0%	(N = 4586)	
Mother's age:	%	n	%	n	%	n	
15–19	19.7	238	21.3	718	20.9	957	
20–24	33.2	401	33.7	1138	33.6	1540	
25–34	41.9	506	38.7	1305	39.5	1812	
35–49	5.2	63	6.3	214	6.0	277	
Parity:							
1	38.5	465	40.1	1352	39.6	1818	
2–3	50.3	609	45.1	1524	46.5	2132	
4+	11.2	136	14.8	500	13.9	636	<0.1
Mother's education:							
None	11.8	143	15.1	508	14.2	651	
Primary	28.6	346	27.7	936	28.0	1283	
Secondary+	59.6	721	57.2	1931	57.8	2652	
Division:							
Barisal	6.1	74	5.7	192	5.8	267	
Chittagong	17.5	212	23.4	791	21.9	1003	
Dhaka	40.2	486	33.6	1135	35.4	1621	
Khulna	8.6	104	7.7	259	7.9	363	
Rajshahi	9.0	109	10.5	353	10.1	462	
Rangpur	9.5	114	9.8	332	9.7	446	
Sylhet	9.1	110	9.3	314	9.2	424	
Residence:							
Urban	26.2	317	26.1	881	26.1	1198	
Rural	73.8	893	73.9	2495	73.9	3388	
Wealth:							
Poorest	22.1	268	21.6	730	21.8	997	
Second	17.6	213	19.5	659	19.0	872	
Middle	19.7	238	18.7	632	19.0	870	
Fourth	22.0	266	20.0	675	20.5	942	
Richest	18.6	225	20.2	680	19.7	905	
Estimated size at birth:							
Small	22.7	275	18.9	637	19.9	912	
Average	65.5	793	67.9	2291	67.3	3084	
Large	11.7	142	13.2	447	12.8	589	
Delivery location:							
Home	58.0	701	62.8	2121	61.6	2822	
Health facility	38.6	466	34.8	1175	35.8	1641	
Public	15.5*	187	12.1	409	13.0	596	
Private	23.1*	279	22.7	767	22.8	1046	
Other	3.4	41	2.4	80	2.6	121	
Attendant at delivery:							
Doctor/midwife/nurse	33.3	402	31.7	1064	32.1	1465	
Unskilled provider/friend/ family member/other	66.7	803	68.3	2293	67.9	3096	
Caesarean delivery:							
Yes	23.3	281	24.2	817	24.0	1099	
No	76.7	928	75.8	2558	76.0	3486	

*Percentages of total deliveries.

Table 3. Survey–weighted logistic regression analysis of early breastfeeding on skin–to–skin contact for the most recent birth, controlling for maternal and infant characteristics

Characteristic	Nigeria (N = 11 419)		Bangladesh (N = 4262)	
Predictor variable	OR	95% CI	OR	95% CI
Skin–to–skin contact	1.42‡	1.15, 1.76	1.27*	1.04, 1.55
Delivery characteristics				
Facility delivery:				
No	NA		1.00	
Yes			0.70*	0.53, 0.92
Caesarean delivery:				
No	NA		1.00	
Yes			0.33‡	0.26, 0.43
Estimated size at birth:				
Small	1.00		1.00	
Average	1.10	0.94, 1.28	1.06	0.87, 1.31
Large	1.08	0.92, 1.26	0.96	0.68, 1.35
Attendant at delivery:				
Unskilled provider/friend/family member/other	1.00		1.00	
Doctor/midwife/nurse	1.03	(0.78, 1.37)	1.43	0.98, 2.09
Maternal demographic characteristics				
Age:				
15–19	1.00		1.00	
20–24	1.07	0.86, 1.32	1.14	0.92, 1.42
25–34	1.15	0.92, 1.45	0.94	0.73, 1.20
35–49	1.23	1.02, 1.50	0.74	0.44, 1.25
Parity:				
1	1.00		1.00	
2–3	1.23*	1.02, 1.50	1.08	0.90, 1.31
4+	1.18	0.95, 1.47	1.04	0.75, 1.43
Zone/Division:				
Nigeria Bangladesh				
North Central Barisal	1.00		1.00	
North East Chittago	1.21	0.95, 1.55	0.83	0.60, 1.14
North West Dhaka	0.58‡	0.46, 0.73	1.15	0.80, 1.64
South East Khulna	0.45†	0.28, 0.71	0.81	0.57, 1.14
South South Rajshahi	0.92	0.71, 1.18	1.22	0.88, 1.70
South West Rangpur	0.40‡	0.28, 0.57	1.50*	1.03, 2.17
Sylhet			1.42*	(1.02, 1.96)
Residence:				
Rural	1.00		1.00	
Urban	1.91‡	1.49, 2.43	0.85	0.67, 1.08
Education:				
None	1.00		1.00	
Primary	1.07	0.91, 1.26	0.90	0.66, 1.22
Secondary+	1.05	0.86, 1.28	0.86	0.65, 1.13
Wealth:				
Poorest	1.00		1.00	
Second	1.30‡	1.08, 1.58	0.85	0.66, 1.10
Middle	1.37*	1.08, 1.75	0.93	0.70, 1.26
Fourth	1.59†	1.20, 2.11	1.13	0.84, 1.52
Richest	1.47*	1.00, 2.16	1.06	0.75, 1.51
Marital status:				
Not married	1.00		1.00	
Married	0.96	0.76, 1.21	1.00	0.41, 2.44

*P<0.05.
†P<0.01.
‡P<0.001.

DISCUSSION

SSC is a natural intervention with numerous benefits, yet it is under–practiced as many mothers and new-borns are separated after birth often due to routine procedures [5,13–15]. SSC has been studied as part of trials, but this is the first analysis to use population–level data to look at coverage and factors related to coverage. Associations between SSC with the early initiation of breastfeeding were also studied given the numerous benefits of early breastfeeding, including reduced infant mortality [20,21]. SSC is also con-sidered step 4 of 10 Steps to Successfully Breastfeeding promoted by the Baby Friendly Hospital Initiative [22].

In our study, we found low coverage of SSC in both Nigeria (10%) and Bangladesh (26%) and few differ-ences between newborns receiving SSC and those not receiving SSC. Though an uncommon interven-tion, in the regression models SSC was significantly associated with early initiation of breastfeeding in both Nigeria and Bangladesh. Thus, our results support findings from trials indicating that SSC is associ-ated with improved breastfeeding outcomes [5] and specifically with early breastfeeding.

Another key finding from the first regression models was that in Bangladesh newborns born in a health facility were less likely to experience early breastfeeding than those born in non–facility environments. There are several plausible explanations for this finding. Some of the mothers and babies may have gone to the facility because of a complication, and this complication may have required separation beyond one hour. A second possible explanation involves health facility procedures, which often require the immedi-ate separation of mother and newborns, which in turn prevents both SSC and early breastfeeding. Many maternal and newborn assessments can actually be done during SSC or can be delayed until after the critical SSC period, so long as the mother and newborn do not have any complications [16,23–25]. Find-ings from Bangladesh revealed that newborns of mothers who had a Cesarean section were significantly less likely to be breastfed early. Other studies have found the same results [26,27], but there is an increas-ing recognition that health facilities must implement protocols that allow mothers who have a Cesarean section to breastfeed early. The Baby Friendly Hospital Initiative recommends that SSC can actually begin in the operating theater (after a Cesarean section) when the mother is alert [22,25].

Skilled delivery in a health facility is promoted as an essential strategy to improve both maternal and new-born health [28,29]. The ideal situation would be for women to deliver in a health facility with a SBA who can oversee SSC, as mother and baby should be monitored in case any complication or safety con-cerns should arise [30].

Other significant findings from the regression analyses are also worthy to note. In both countries there were some differences by zone or division. In Nigeria the northern zones are generally poorer than the southern zones. However early breastfeeding was less common in the southern zones than in the North Central zone. A study by Berde and Yalcin also found variation in the early initiation of breastfeeding by zone [31]. Our results from Bangladesh indicated that early breastfeeding was more common in Rangpur and Sylhet, the poorest divisions, compared to Barisal. A systematic review of early breastfeeding in South Asia also found geographic differences in the early initiation of breastfeeding within countries and also highlighted the influence of traditional practices, which may vary within countries [32]. Another system-atic review highlighted the importance of the knowledge and beliefs of family members, particularly for women who deliver at home [33]. A study from Nepal attributed variations in early breastfeeding to many factors including socioeconomic factors, geographic terrain and the availability of formula [34]. Our find-ings from Nigeria suggested that wealthier and urban women as well as those of parity 2 or 3, had in-creased odds of having their newborns initiate breastfeeding early. These women may have greater knowl-edge than their counterparts and some previous experience with breastfeeding. Perceived size at birth was not significant in our regression analyses, but other studies have found that low birthweight and prema-ture newborns are less likely to be breastfed early than normal weight and term newborns [32,33]. Taken together, these comprehensive findings suggest that there is a need to ensure equitable diffusion of knowl-edge on the importance of early breastfeeding and SSC to all delivery attendants and to all women and families regardless of wealth, parity or geographic residence.

There are several limitations to this analysis. The questions on SSC were not the same for the two coun-tries, and SSC was only asked to women who had a non–facility delivery in Nigeria. More broadly addi-tional work may be needed to validate measures of SSC. A validation study by Blanc et al. 2016 [35] in Kenya found that questions on SSC (newborn placed against mother's chest after delivery and newborn was naked on skin, not wrapped in towel) did not perform well in terms of individual–level reporting accuracy and population–level accuracy. In this study women's reports before discharge were compared

to direct observation in two hospitals. However, Stanton et al. 2013 [36] found that a question on SSC met the criteria for quality reporting in study in Mozambique, which compared women's reporting in household surveys (8 to 10 months after delivery) to direct observations. Further work may be needed on exact wording for questions on SSC and for appropriate probes. Another limitation is that the DHS data did not yield complete information on actual birthweight, which is often unknown for newborns who are born at home and not weighed. Also lacking were information on maternal and newborn complications as well as quality of care at the facilities and characteristics of providers. Recall bias could also be an issue in that mothers were asked to recall an event that occurred in a one–hour period. Some of the mothers had births several years (three to five) before the survey.

In terms of program recommendations, training of SBAs on proper thermal care for newborns including SSC is a key step in improving newborn health. The WHO's Essential Newborn Training Guide includes modules on thermal care including SSC [6]. Manasyan et al. 2011 found this training to be cost–effective for midwives at first level health facilities in Zambia [37]. Trainings will need to be done on a large scale to ensure that all healthy newborns, regardless of delivery type (vaginal vs Cesarean), size or socioeconomic status, receive SSC. At the same time community engagement is needed to enable more mothers and families to learn about the protective effects of SSC. More research is needed on exact timing of initiation of SSC, frequency and duration as well as measures to ensure SSC is as safe as possible [5]. SSC is an intervention with the potential to save newborn lives.

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Does postnatal care have a role in improving newborn feeding? A study in 15 sub–Saharan African countries

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Background Breastfeeding is known as a key intervention to improve newborn health and survival while prelacteal feeds (liquids other than breastmilk within 3 days of birth) represents a departure from optimal feeding practices. Recent programmatic guidelines from the WHO and UNICEF outline the need to improve newborn feeding and points to postnatal care (PNC) as a potential mechanism to do so. This study examines if PNC and type of PNC provider are associated with key newborn feeding practices: breastfeeding within 1 day and prelacteal feeds.

Methods: We use data from the Demographic and Health Surveys for 15 sub–Saharan African countries to estimate 4 separate pooled, multilevel, logistic regression models to predict the newborn feeding outcomes.

Findings: PNC is significantly associated with increased breastfeeding within 1day (OR = 1.35, $P<0.001$) but is not associated with PLFs (OR = 1.04, $P=0.195$). PNC provided by nurses, midwives and untrained health workers is also associated with higher odds of breastfeeding within 1 day of birth (OR = 1.39, $P<0.001$, (OR = 1.95, $P<0.001$) while PNC provided by untrained health workers is associated with increased odds of PLFs (OR = 1.20, $P=0.017$).

Conclusions: PNC delivered through customary care may be an effective strategy to improve the breastfeeding within 1 day but not to discourage PLFs. Further analysis should be done to examine how these variables operate at the country level to produce finer programmatic insight.

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Breastfeeding is recognized as a key intervention to improve the health and survival of children and the use of optimal breastfeeding practices such as exclusive breastfeeding is one of the most effective means to reduce undernutrition, an underlying cause of under–five mortality [1]. The World Health Organization (WHO) and the United National Children's Fund (UNICEF) recommend early initiation of breastfeeding [2] which refers to breastfeeding of a newborn within an hour of birth. Global monitoring efforts by UNICEF also include initiation of breastfeeding within one day of birth which provides additional information on the feeding patterns of newborns and the behaviors of women. Early initiation of breastfeeding has a number of health benefits, one of which is to reduce neonatal mortality [3–5]. The early ingestion of breastmilk can have positive effects on a newborn's immune systems such as the provision of immunoglobulins and lymphocytes [6–8], priming of the gastrointestinal tract and decreasing the permeability of the tract to pathogens, including HIV [9,10]. Another health benefit of early initiation of breastfeeding is reduced rates of diarrhea among infants, as demonstrated in Egypt and Pakistan [11,12].

Early initiation of breastfeeding is also associated with a number of factors. One such factor is skin–to–skin contact with the mother [13,14], a form of thermal care which is a recommended means to reduce neonatal mortality [15]. Early breastfeeding is also associated with a number of factors related to contact with the health system. For example, in Brazil, early initiation is associated with vaginal delivery as well as other factors such as antenatal guidance on breastfeeding and having a full term pregnancy [16]. Other studies point out that breastfeeding within an hour of birth is less likely to occur when women have caesarian sections, even in the presence of hospital practices that favor breastfeeding [17,18]. In a review article, authors find that higher socio–economic status is associated with lower odds of breastfeeding initiation but this pattern is only seen in developing countries [19].

Prelacteal feeds (PLFs) represent a departure from optimal newborn feeding practices. PLFs are any liquid other than breast milk that is given to the newborn before breastfeeding is established between the mother and newborn. The WHO and UNICEF outline that for successful breastfeeding, PLFs should be avoided and PLFs should not be encouraged unless medically indicated [20]. These feeds usually occur within the first few days of life and are associated with a number of negative health outcomes for the newborn and mother. These include insufficient maternal milk production, newborn diarrhea and reduced length of breastfeeding duration [21,22]. PLFs can also expose newborns to infections through the ingestion of contaminated food and liquids which can act on the GI tract to increase permeability to pathogens, and hence, increase newborn infections [9,11].

A number of studies have shown factors related to PLFs. For example, PLFs are negatively associated with early initiation of breastfeeding (within an hour of birth) [23]. In India, PLFS were associated with lower maternal education among hospital–delivered infants [24]. However, in rural, Western Uganda, more educated women were more prone to provide PLFs to newborns [25]. In low socio–economic settlements in Karachi, Pakistan, PLFs were associated with having a birth attendant [26]. In a national study in Nepal, women without education, who were not working, who had no antenatal care and were first time mothers were more likely to provide PLFs [27]. Both in India and Vietnam, newborns of women with a cesarean section were more likely to ingest PLFs [24,28].

In a recent joint statement, the WHO and UNICEF recommend that all newborns, regardless of place of birth (whether in a facility or not), should receive a basic package of care, including postnatal care which includes the promotion and support of exclusive breastfeeding and the early initiation of breastfeeding [29]. Interventions such as thermal care, hygienic cord care, examination for danger signs and improving parental knowledge of care seeking are also recommended. The evidence on the importance of PNC from developing countries comes mainly from South Asian countries (India, Bangladesh and Pakistan) and are from interventions and trials at sub–national levels (such as districts, villages and communities) [30–32].

Currently, there is a gap in the literature on how interventions such as PNC are associated with newborn feeding practices at the national level, when delivered through usual services of the government and non–governmental sources of care ie, outside of an intervention setting. The literature is especially sparse for sub–Saharan Africa. The only study we found was a small, cross–sectional study in Ethiopia [33] where PNC was associated with increased odds of timely initiation of breastfeeding. Apart from the issue of generalizability of PNC interventions, we currently do not know which type of provider of PNC is best suited to improve the newborn feeding outcomes. The WHO–UNICEF PNC recommendation acknowledges that skilled and unskilled health workers can provide PNC though skilled providers are better suited [29]. However, in the literature on newborn feeding, we find varying opinions on if skilled or unskilled care can improve breastfeeding. In Bangladesh, for example, specially trained peer counselors can improve initiation and duration of exclusive breastfeeding [34]. However, a literature review finds that trained health care workers (physicians, nurses etc.) were found to be a barrier to providing quality information, counseling and care to women on early breastfeeding [19].

The main objective of this paper is to examine the association between PNC within 1 day and two key newborn feeding practices: breastfeeding within 1 day and prelacteal feeds. Given that WHO–UNICEF recommends both skilled and unskilled health workers to provide PNC and that there are mixed results regarding the association of provider type on newborn feeding, we also examine if the type of provider of PNC is important for the two stated outcomes. We use data from nationally representative surveys in 15 sub–Saharan African countries in a pooled, multi–level analysis, controlling for a number of individual and country–level variables. The results of this paper can provide indications on which types of providers are best suited for the delivery of PNC as it relates to newborn feeding.

METHODS

Data and variables

Data for this study are from the USAID–supported Demographic and Health Surveys (DHS). DHS surveys collect data from nationally–representative probability samples of households. Households are selected using a two–stage sample design where census enumeration areas are first selected and then a random sample of households is selected in the second stage. Within selected households, all women ages 15–49 are interviewed and provide information on themselves and their children on various health, population and nutrition issues. Women also provide informed consent to the survey prior to the start of questions. All data are anonymized. This analysis focuses on the last birth in the last two years before the surveys for which information on PNC is provided. We include Benin 2011–2012, Burkina Faso 2010, Comoros 2012, Congo Brazzaville 2012, Cote d'Ivoire 2012, Gabon 2012, Guinee 2012, Mali 2012–2013, Namibia 2013, Niger 2012, Nigeria 2013, Sierra Leone 2013, Tanzania 2010, Uganda 2011 and Zimbabwe 2011, based on the availability of comparable data on PNC.

There are two outcome variables. The first is the percentage of newborns who were breastfed within 1 day of birth among all newborns. The second outcome variable is the percentage of newborns who received a PLF ie, a feed that occurs within 3 days of births that is not breastmilk. The measure of PLFs is based on asking the mother if, within the first 3 days after delivery, the newborn was given anything to drink, other than breast milk. This is only asked for newborns who were ever breastfed.

The key independent variable is PNC within 1 day which refers to any check within 1 day to a newborn following birth. The question also provides examples of what a check may entail (checking temperature, cord etc.). We exclude a check by 'others' (such as friends or relatives as these are not likely to be medical). Women were also asked, if for the last birth in the 2 years before the survey, what provider or traditional birth attendant performed the check on the newborn's health. Qualitative work confirms that women are able to tell coherent narratives about the moments around birth and recognize checks on the health of a child [35]. Given that PLFs can occur anytime within 3 days, we attempt to establish PNC preceding PLFs by defining PNC as a check within 1 day of birth instead of 3 days. Both of these outcomes are binary. To investigate if PNC provider is associated with the outcomes, we create a variable for PNC provided by three categories of caregivers: physicians, nurses/midwives/auxiliary midwives and finally, traditional birth attendants/community health workers/other.

In our models, we introduce a number of statistical controls based on the literature, classified as individual–level controls or country–level controls. We include: age of the mother, previous birth interval, parity, caesarian section of birth, use of antenatal care (ANC), receipt of tetanus toxoid vaccination, skilled delivery, educational level of the woman, marital status, media access (regular access to print and mass media), place of residence and a wealth index of household goods and assets (provided in the DHS data files), constructed using Principal Component Analysis of household–level ownership of goods and assets.

We include 4 binary, country–level variables to account for the variation in the supply of PNC. The five country–level variables are: Gross Domestic Product (GDP) per capita ("high" when US\$ 1000 or greater per capita or "low" when below US\$ 1000 per capita), per capita government expenditure on health ("high" when US\$ 100 or greater per capita and "low" when below US\$ 100 per capita), number of physicians per 1000 population ("high" when the value is 0.1 or greater and "low" when the value is below 0.1) and finally, the number of nurses per 1000 population ("high" when the value is 1 and greater and "low" when the value is less than 1). Finally, since there are prominent recommendations on newborn feeding practices in areas of high HIV prevalence, we included a dummy variable for HIV prevalence ("high" when 5% or greater and "low" when less than 5%) as an explanatory variable in the models.

Statistical analysis

We use descriptive statistics and multivariate models to examine the association between the main predictors and the outcomes. First, we describe the sample using frequencies of the variables and then produce cross–tabulations of key variables by the outcome variables using chi–square tests. Finally, we model the outcome variables on the key variables (in separate models), with a number of statistical controls. Univariate analysis is done at the country level to provide an indication of the contribution of each country to overall sample but as the aim of the analysis is cross–country, the remainder of the analysis is done at the aggregate level.

As breastfeeding within 1 day and PLFs are binary outcomes, a logistic regression model can be used, assuming that the error term follows a logistic distribution. However, as we study individual–level data from different countries, this suggest that these data are clustered and as a consequence, a multilevel model may be required (MLM). To verify if MLM is needed, we compared all MLMs to single level logistic regressions using a Likliehood–ratio (LR) test. These results should that the data are clustered at the country level and that MLMs perform better than the single–level logistic regressions. In our models, country–level variance was between 4 to 11 percent. Multilevel models and bivariate table are run without sample weights while univariate are weighted using DHS sample weights provided in datafiles.

RESULTS

Breastfeeding within a day of birth is high (81 percent) and varies considerably across the countries, ranging from 66 percent in Cote d'Ivoire to 94 percent in Mali (**Table 1**). Levels of prelacteal feeds are lower (39 percent overall), ranging from 11 percent in Namibia to 65 percent in Cote d'Ivoire. PNC is low overall; only 15 percent of the sample received PNC within a day, of which the vast majority was provided by a nurse (12 percent) and only 2 and 1 percent provided by physicians and by traditional birth attendants/community health workers/others (TBA/CHWs/others) respectively. In the sample, about half of the women had 3 or fewer children. Caesarian sections are uncommon (4 percent). More than half of the women had contact with the health system through ANC care (52 percent), receipt of tetanus toxoid (56 percent) and had a skilled delivery (62 percent). The majority of the sample is married, has no education, no regular access to media and about 40 percent is classified into the poorest or second lowest wealth quintiles.

In 7 of the 15 countries, newborns who receive PNC were more likely to be breastfed within 1 day compared with newborns who did not receive PNC but in several countries (eg, Comoros, Congo (Brazzaville), Uganda), the opposite occurs (**Figure 1**). **Figure 2** shows that while overall newborns receiving
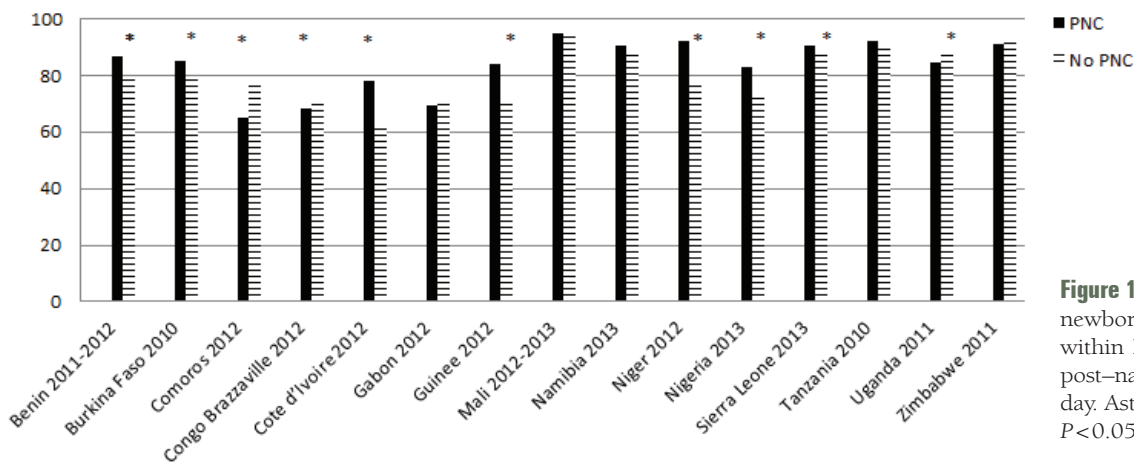
Figure 1. Percentage of newborns breastfed within 1 day of birth by post–natal care within 1 day. Asterisk indicates $P < 0.05$.
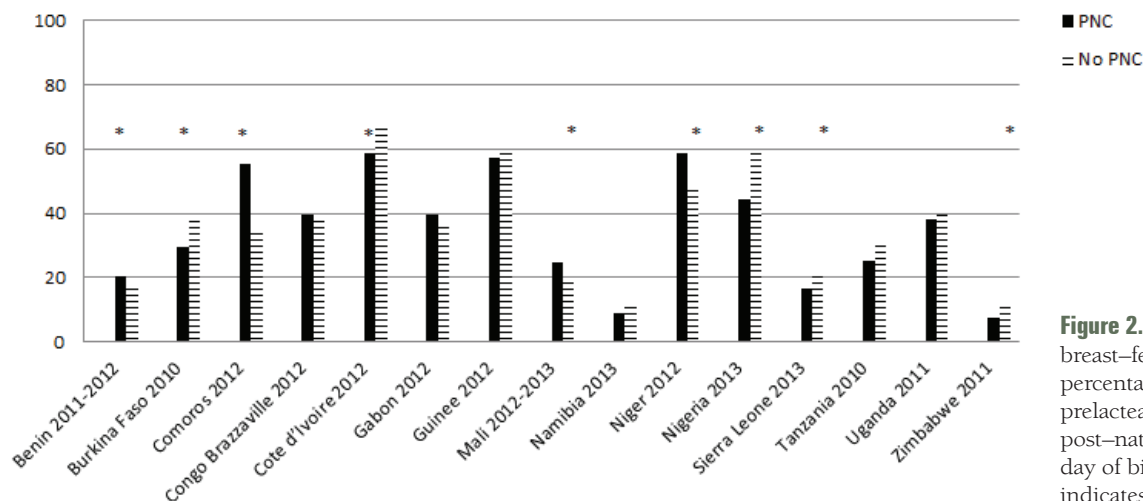
Figure 2. Among ever breast–fed newborns, percentage who had a prelacteal feed by post–natal care within 1 day of birth. Asterisk indicates $P < 0.05$.

Table 1. Weighted distribution of sample for 15 countries

	Benin 2011–2012	Burkina Faso 2010	Comoros 2012	Congo Brazzaville 2012	Cote d'Ivoire 2012	Gabon 2012	Guinee 2012	Mali 2012–2013
Outcomes								
Breastfeeding within 1 d of birth:								
Yes	80.9	80.5	76.3	69.8	66.2	70.0	73.1	94.0
No	19.1	19.5	23.7	30.2	33.8	30.0	26.9	6.0
Prelacteal feeding:*								
Yes	18.1	35.9	37.5	36.1	65.6	41.3	59.1	21.1
No	81.9	64.1	62.5	63.9	34.4	58.7	40.9	78.9
Key variables								
PNC within 1 d:								
Yes:	20.6	18.0	10.3	15.4	24.8	12.7	16.7	13.5
By Physician	2.0	0.2	1.6	2.7	2.7	1.2	4.4	1.7
By Nurse/Midwife/Aux. midwife	17.4	17.5	8.2	12.6	17.5	11.2	9.5	7.2
By TBA/CHW/Other	1.1	0.2	0.6	0.1	4.6	0.2	2.8	4.5
No	79.4	82.0	89.7	84.6	75.2	87.3	83.3	86.5
Maternal factors								
Age of mother:								
15–19	6.2	8.6	8.5	14.0	12.2	14.9	14.3	11.3
20–24	22.1	26.6	22.7	25.8	26.3	25.8	23.1	22.9
25–29	31.8	25.3	24.4	25.8	27.3	24.3	25.4	28.6
30–34	22.1	19.9	23.5	18.1	18.7	18.3	17.1	19.2
35–39	12.0	12.9	15.1	12.6	10.1	11.1	12.8	12.1
40–49	5.7	6.8	5.8	3.8	5.4	5.6	7.3	5.8
Previous birth interval:								
First birth (and twins)	20.8	17.6	22.4	23.7	22.5	27.9	21.2	17.1
<18 months	2.6	1.9	9.2	3.4	3.1	4.8	1.4	3.9
18–23 months	6.5	6.0	12.4	7.3	6.1	8.7	5.7	8.1
24–29 months	13.8	13.2	13.7	12.6	13.1	11.7	9.5	14.4
30–35 months	14.0	17.7	10.7	10.2	13.2	8.1	15.7	14.2
36–47 months (ref)	20.3	23.4	13.6	15.0	16.4	12.0	21.1	20.2
48–53 months	6.2	6.0	4.9	6.1	5.3	4.7	7.2	5.7
54+ months	15.7	14.2	13.1	21.7	20.3	22.1	18.3	16.4
Parity:								
1	20.5	17.5	22.1	23.4	22.1	27.6	21.1	17.0
2–3	38.7	33.8	35.3	42.4	37.3	38.2	33.0	33.4
4–5	24.5	23.3	23.6	22.9	22.8	20.1	23.5	27.1
6+	16.3	25.3	19.0	11.2	17.7	14.1	22.4	22.5
Cesarean section:								
Yes	6.1	2.1	11.4	6.6	3.0	10.6	3.0	3.0
No	93.9	97.9	88.6	93.4	97.0	89.4	97.0	97.0
Personal illness control factors								
Antenatal care (4+ with any provider):								
Yes	58.7	32.5	47.6	76.0	42.8	75.6	56.2	41.0
No	41.3	67.5	52.4	24.0	57.2	24.4	43.8	59.0
Tetanus toxoid (2+ during last pregnancy):								
Yes	59.4	70.3	36.2	59.9	52.1	66.5	70.1	36.8
No	40.6	29.7	63.8	40.1	47.9	33.5	29.9	63.2
Skilled delivery:								
Yes	85.6	74.2	85.6	94.1	61.4	91.2	46.2	61.2
No	14.4	25.8	14.4	5.9	38.6	8.8	53.8	38.8
Socio–economic factors								
Education of mother:								
None	69.7	83.4	43.3	7.0	62.4	5.8	75.5	81.6
Primary	16.7	10.8	24.9	31.1	26.5	25.9	13.6	9.1
Secondary+	13.6	5.7	31.8	61.9	11.2	68.3	10.9	9.3
Marital status:								
Married/cohabiting	93.6	97.1	94.5	78.3	83.4	70.3	92.3	96.7
Not currently married/cohabiting	6.4	2.9	5.5	21.7	16.6	29.7	7.7	3.3
Media access:								
Yes	22.5	9.2	26.6	25.9	17.0	46.7	17.0	23.7
No	77.5	90.8	73.4	74.1	83.0	53.3	83.0	76.3

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Table 1. Continued

	Benin 2011–2012	Burkina Faso 2010	Comoros 2012	Congo Brazzaville 2012	Cote d'Ivoire 2012	Gabon 2012	Guinee 2012	Mali 2012–2013
Household wealth status:								
Poorest quintile	20.3	20.2	23.0	22.2	24.3	21.3	22.9	20.4
Second quintile	20.5	21.9	20.8	23.0	20.4	21.6	21.4	20.2
Middle quintile	19.4	22.0	21.1	20.2	20.7	22.5	20.7	19.4
Fourth quintile	19.7	21.0	18.5	19.0	18.6	19.3	19.1	22.1
Richest quintile	20.1	14.9	16.6	15.5	15.9	15.2	15.9	17.8
Residence:								
Urban	41.3	17.0	28.4	61.4	38.7	84.3	26.5	20.3
Rural	58.7	83.0	71.6	38.6	61.3	15.7	73.5	79.7
Country–level characteristics								
GDP per capita (US$):								
High (1000 per capita and greater)	–	–	–	–	–	–	–	–
Low (less than 1000 per capita)	–	–	–	–	–	–	–	–
Per capita government expenditure on health at average exchange rate (US$):								
High (100 per capita and greater)	–	–	–	–	–	–	–	–
Low (less than 100 per capita)	–	–	–	–	–	–	–	–
No. physicians per 1000 population:								
High (0.1 or greater)	–	–	–	–	–	–	–	–
Low (less than 0.1)	–	–	–	–	–	–	–	–
No. nurses per 1000 population:								
High (1 or greater)	–	–	–	–	–	–	–	–
Low (less than 1)	–	–	–	–	–	–	–	–
HIV prevalence:								
High (5%+)	–	–	–	–	–	–	–	–
Low (<5%)	–	–	–	–	–	–	–	–
Total	5130	5988	1298	3426	3039	2102	2818	3965

	Namibia 2013	Niger 2012	Nigeria 2013	Sierra Leone 2013	Tanzania 2010	Uganda 2011	Zimbabwe 2011	All countries
Outcomes								
Breastfeeding within 1 d of birth:								
Yes	89.1	78.6	73.7	89.1	90.5	88.7	91.7	80.1
No	10.9	21.4	26.3	10.9	9.5	11.3	8.3	19.8
Prelacteal feeding:*								
Yes	10.2	49.1	58.4	20.7	30.8	41.1	13.1	39.1
No	89.8	50.9	41.6	79.3	69.2	58.9	86.9	60.9
Key variables								
PNC within 1 d:								
Yes:	15.3	10.7	11.4	26.4	1.2	8.8	9.5	14.6
By Physician	5.6	0.2	4.5	1.5	0.1	1.8	1.6	2.3
By Nurse/Midwife/Aux. midwife	9.5	8.8	5.9	21.0	0.9	6.7	7.7	10.9
By TBA/CHW/Other	0.2	1.7	1.0	3.9	0.2	0.3	0.2	1.5
No	84.7	89.3	88.6	73.6	98.8	91.2	90.5	85.4
Maternal factors								
Age of mother:								
15–19	10.7	9.6	8.5	13.5	10.2	10.3	12.4	10.4
20–24	25.5	23.1	22.7	23.0	27.1	28.2	31.2	24.5
25–29	25.5	27.4	28.0	26.1	25.4	27.5	27.6	27.1
30–34	20.1	20.8	20.1	18.0	17.5	16.2	16.3	19.3
35–39	12.3	13.0	13.4	12.9	14.2	12.5	9.0	12.6
40–49	5.9	6.1	7.3	6.5	5.5	5.4	3.5	6.1
Previous birth interval:								
First birth (and twins)	32.2	13.6	20.3	22.0	19.9	17.2	29.3	20.7
<18 months	2.4	4.1	4.1	2.5	3.6	6.1	2.4	3.5
18–23 months	4.9	11.3	9.9	6.9	8.0	12.9	3.6	8.1
24–29 months	8.2	20.6	15.7	12.0	16.9	20.5	6.8	14.3
30–35 months	7.7	18.1	15.1	13.9	15.6	13.7	8.7	14.2
36–47 months (ref)	9.8	18.3	18.1	16.7	16.0	15.0	14.9	17.8
48–53 months	4.9	4.3	4.4	5.7	5.0	3.4	5.8	5.2
54+ months	29.8	9.7	12.4	20.4	14.9	11.1	28.5	16.3

Table 1. Continued

	Namibia 2013	Niger 2012	Nigeria 2013	Sierra Leone 2013	Tanzania 2010	Uganda 2011	Zimbabwe 2011	All countries
Parity:								
1	31.7	13.4	20.1	21.7	19.6	17.1	29.0	20.4
2–3	42.7	27.4	32.3	35.0	35.7	31.5	47.4	35.1
4–5	17.4	24.6	22.6	24.8	23.2	22.4	16.6	23.1
6+	8.2	34.5	25.0	18.6	21.5	29.0	6.9	21.4
Cesarean section:								
Yes	15.7	1.4	2.2	4.0	5.2	5.5	4.5	4.3
No	84.3	98.6	97.8	96.0	94.8	94.5	95.5	95.7
Personal illness control factors								
Antenatal care (4+ with any provider):								
Yes	62.0	33.1	51.1	76.0	38.4	46.2	59.2	51.4
No	38.0	66.9	48.9	24.0	61.6	53.8	40.8	48.6
Tetanus toxoid (2+ during last pregnancy):								
Yes	33.9	50.2	48.7	86.7	44.1	52.2	42.8	55.4
No	66.1	49.8	51.3	13.3	55.9	47.8	57.2	44.6
Skilled delivery:								
Yes	89.0	33.4	42.4	62.6	49.7	60.9	64.9	61.6
No	11.0	66.6	57.6	37.4	50.3	39.1	35.1	38.4
Socio–economic factors								
Education of mother:								
None	5.6	85.3	47.6	64.7	25.6	12.9	1.1	51.8
Primary	22.5	9.6	18.1	15.3	67.0	63.9	31.3	22.7
Secondary+	71.9	5.1	34.3	20.1	7.4	23.2	67.5	25.5
Marital status:								
Married/cohabiting	44.2	98.3	95.6	84.7	84.0	85.5	87.3	89.3
Not currently married/cohabiting	55.8	1.7	4.4	15.3	16.0	14.5	12.7	10.7
Media access:								
Yes	34.9	7.4	22.2	7.5	18.0	16.0	19.8	19.1
No	65.1	92.6	77.8	92.5	82.0	84.0	80.2	80.9
Household wealth status:								
Poorest quintile	21.3	19.3	23.2	23.0	21.0	22.4	22.2	21.8
Second quintile	22.6	20.5	22.8	21.0	23.9	22.0	21.1	21.7
Middle quintile	21.7	20.8	18.9	21.9	21.7	19.5	19.5	20.4
Fourth quintile	20.0	21.1	18.0	19.1	18.8	18.1	21.2	19.5
Richest quintile	14.4	18.3	17.1	14.9	14.6	18.0	16.0	16.6
Residence:								
Urban	47.5	13.5	35.3	25.7	20.9	14.6	29.3	31.5
Rural	52.5	86.5	64.7	74.3	79.1	85.4	70.7	68.5
Country–level characteristics								
GDP per capita (US$):								
High (1000 per capita and greater)								
Low (less than 1000 per capita)	–	–	–	–	–	–	–	37.7
Per capita government expenditure on health at average exchange rate (US$):	–	–	–	–	–	–	–	62.3
High (100 per capita and greater)	–	–	–	–	–	–	–	50.7
Low (less than 100 per capita)	–	–	–	–	–	–	–	49.3
No. physicians per 1000 population:								
High (0.1 or greater)	–	–	–	–	–	–	–	43.9
Low (less than 0.1)	–	–	–	–	–	–	–	56.1
No. nurses per 1000 population:								
High (1 or greater)	–	–	–	–	–	–	–	36.2
Low (less than 1)	–	–	–	–	–	–	–	63.8
HIV prevalence:								
High (5%+)	–	–	–	–	–	–	–	17.6
Low (<5%)	–	–	–	–	–	–	–	82.4
Total	1947	5143	12473	4820	3266	3092	2448	60956

PNC – postnatal care, TBA – Traditional Birth Attendant, CHW – Community Health Worker

*Denominator is ever–breast fed newborns.

PNC are significantly less likely to receive a prelacteal feed, patterns by country vary considerably; 5 countries show a statistically significant relationship but 4 show the opposite pattern.

In the bivariate analysis, newborns receiving PNC within 1 day are significantly more likely to initiate breastfeeding within a day and less likely to receive a prelacteal feed (**Table 2**). Women receiving antena

Table 2. Percentage of all newborns breastfed within 1 day and percentage of newborns receiving prelacteal feeds among ever breastfed newborns, by key characteristics (unweighted), 15 countries

	ALL NEWBORNS		EVER BREASTFED NEWBORNS	
	Breastfeeding within:		Prelacteal feed	
	1 day	P		P
Key dependent variables				
PNC within 1 day:				
Yes	84.2	<0.001	35.3	<0.001
No	79.8		39.3	
Maternal factors				
Age of mother:				
15–19	76.3	<0.001	42.5	<0.001
20–24	80.1		38.9	
25–29	81.9		37.0	
30–34	81.4		37.7	
35–39	80.8		38.6	
40–45	80.4		40.7	
45–49	79.9		45.3	
Previous birth interval:				
First birth (and twins)	81.8	<0.001	38.7	<0.001
<18 months	76.8		39.6	
18–23 months	78.2		41.6	
24–29 months	80.5		41.6	
30–35 months	82.1		40.7	
36–47 months	81.8		39.7	
48–53 months	81.5		35.7	
54+ months	81.5		33.7	
Parity:				
1	77.0	<0.001	39.6	<0.001
2–3	81.9		35.6	
4–5	82.2		38.2	
6+	79.9		43.2	
Cesarean section:				
Yes	62.4	<0.001	38.3	0.710
No	81.3		38.7	
Breastfed within 1 hour:				
Yes	–		28.0	<0.001
No	–		47.3	
Personal illness control factors				
Antenatal care (4+ with any provider):				
Yes	82.0	<0.001	33.9	<0.001
No	78.9		43.8	
Tetanus toxoid (2+ during last pregnancy):				
Yes	81.5	<0.001	35.5	<0.001
No	79.2		42.7	
Skilled delivery:				
Yes	82.8	<0.001	30.9	<0.001
No	76.7		51.4	
Socio–economic factors				
Education of mother:				
None	79.3	<0.001	42.7	<0.001
Primary	82.4		37.1	
Secondary+	81.2		32.2	

Table 2. Continued

	All newborns		Ever breastfed newborns	
	Breastfeeding within:		Prelacteal feed	
Marital status:				
Married/cohabiting	80.7	0.001	39.4	<0.001
Not currently married/cohabiting	79.0		33.2	
Media access:				
Yes	81.6	0.001	33.6	<0.001
No	80.3		39.8	
Household wealth status:				
Poorest quintile	77.2	<0.001	43.2	<0.001
Second quintile	79.2		40.8	
Middle quintile	82.1		38.1	
Fourth quintile	82.3		35.7	
Richest quintile	83.1		33.3	
Residence:				
Urban	81.7	<0.001	34.2	<0.001
Rural	80.0		40.6	
Country characteristics				
GDP per capita (US$):				
High (1000+ per capita)	74.0	<0.001	49.7	<0.001
Low (<1000 per capita)	84.7		31.6	
Per capita government expenditure on health at average exchange rate (US$):				
High (100+ per capita)	77.5	<0.001	44.3	<0.001
Low (<100 per capita)	83.7		32.7	
No. physicians per 1000 population.				<0.001
High (0.1+)	75.7	<0.001	50.6	
Low (<0.1)	84.3		29.2	
No. nurses per 1000 population:				
High (1+)	79.1	<0.001	44.1	<0.001
Low (<1)	81.4		35.6	
HIV prevalence:				
High (5%+)	90.2	<0.001	24.9	<0.001
Low (<5%)	78.5		41.6	
Total	61018		59309	

PNC – postnatal care

tal care, tetanus toxoid and skilled delivery are significantly more likely to breastfeed within a day and less likely to provide a prelacteal feed to the newborn. A caesarian birth is significantly associated with breastfeeding within 1 day but not with PLFs. Women with no education are less likely to breastfeed early and more likely to provide a prelacteal feed. While household wealth is positively associated with breastfeeding within 1 day, the association is negative with prelacetal feeds. Women in urban areas are more likely than rural women to initiate breastfeeding within 1 day and less likely to give a prelacetal feed. Bivariate analysis of the country–level variables also shows lower levels of GDP, expenditures, and physician and nurse density are associated with greater initiation of breastfeeding within 1 day and lower levels of prelacteal feeds. In countries with higher HIV prevalence, breastfeeding within 1 day is higher and prelacteal feeds are lower.

Table 3 shows that after controlling for individual and country–level variables, PNC within 1 day is significantly associated with higher odds of breastfeeding within 1 day (OR = 1.35, 95% CI 1.27–1.44). The odds of breastfeeding within 1 day are significantly lower for women who had a caesarian section compared with those that did not have a caesarian section (OR = 0.26, 95% CI 0.23–0.28). Many of the variables related to contact with the health care system that are significant at the bivariate level are also significant in the multilevel model. These include ANC (OR = 1.07, 95% CI 1.02–1.12), tetanus coverage (OR = 1.10, 95% CI 1.05–1.15) and skilled delivery (OR = 1.48, 95% CI 1.40–1.56). Several socio–economic variables are significantly associated with breastfeeding within 1 day. Compared to women with no education, women with primary education are significantly more likely to initiate breastfeeding within 1 day (OR = 1.10, 95% CI 1.04–1.17) though the association with secondary or higher education is

Table 3. Multilevel logistic regression for breastfeeding within 1 d among all newborns and prelacteal feeds among ever breastfed newborns, 15 countries

Fixed Effects	ALL NEWBORNS, BREASTFEEDING WITHIN 1 D						AMONG EVER BREASTFED NEWBORNS, PRELACTEAL FEEDS					
	Model 1	P	95% CI	Model 2	P	95% CI	Model 3	P	95% CI	Model 4	P	95% CI
Key variables												
PNC within 1 d:												
Yes	1.35	<0.001	1.27–1.44	–	–	–	1.04	0.195	0.98–1.09	–	–	–
No	1.00	–	–	–	–	–	1.00	–	–	–	–	–
Provider of PNC within 1 d:												
By Physician	–	–	–	0.93	0.269	0.81–1.06	–	–	–	0.94	0.343	0.83–1.07
By Nurse/Midwife	–	–	–	1.39	<0.001	1.29–1.50	–	–	–	1.03	0.315	0.97–1.09
By TBA/CHW/Other	–	–	–	1.95	<0.001	1.60–2.36	–	–	–	1.20	0.017	1.03–1.39
No	–	–	–	1.00	–	–	–	–	–	1.00	–	–
Maternal factors												
Age of mother:												
15–19	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
20–24	1.08	0.049	1.00–1.17	1.09	0.043	1.00–1.17	0.93	0.038	0.86–1.00	0.93	0.040	0.86–1.00
25–29	1.15	0.002	1.05–1.26	1.16	0.001	1.06–1.26	0.84	<0.001	0.78–0.91	0.85	<0.001	0.78–0.92
30–34	1.13	0.020	1.02–1.25	1.14	0.014	1.03–1.26	0.85	<0.001	0.77–0.93	0.85	<0.001	0.77–0.93
35–39	1.12	0.050	1.00–1.26	1.13	0.038	1.01–1.27	0.85	0.002	0.77–0.94	0.85	0.002	0.77–0.94
40–49	1.16	0.027	1.02–1.33	1.17	0.020	1.03–1.34	0.91	0.117	0.81–1.02	0.91	0.127	0.81–1.03
Previous birth interval:												
First birth (and twins)	0.35	<0.001	0.24–0.49	0.35	<0.001	0.24–0.50	1.19	0.374	0.81–1.77	1.20	0.374	0.81–1.77
<18 months	0.78	<0.001	0.69–0.88	0.78	<0.001	0.69–0.88	1.07	0.181	0.97–1.19	1.07	0.185	0.97–1.19
18–23 months	0.92	0.070	0.84–1.01	0.92	0.069	0.84–1.01	1.04	0.332	0.96–1.12	1.04	0.332	0.96–1.12
24–29 months	1.01	0.733	0.94–1.09	1.01	0.721	0.94–1.09	1.03	0.399	0.96–1.10	1.03	0.400	0.96–1.10
30–35 months	1.01	0.805	0.94–1.09	1.01	0.813	0.94–1.09	0.98	0.624	0.92–1.05	0.98	0.623	0.92–1.05
36–47 months (ref)	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
48–53 months	0.93	0.190	0.84–1.04	0.93	0.194	0.84–1.04	0.97	0.457	0.88–1.06	0.97	0.455	0.88–1.06
54+ months	0.89	0.003	0.83–0.96	0.89	0.003	0.83–0.96	0.96	0.231	0.90–1.03	0.96	0.230	0.90–1.03
Parity:												
1	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
2–3	0.48	<0.001	0.34–0.68	0.48	<0.001	0.34–0.68	0.97	0.868	0.65–1.43	0.97	0.869	0.65–1.43
4–5	0.49	<0.001	0.34–0.70	0.49	<0.001	0.34–0.71	1.03	0.889	0.69–1.53	1.03	0.891	0.69–1.53
6+	0.45	<0.001	0.32–0.65	0.45	<0.001	0.32–0.65	1.05	0.794	0.71–1.57	1.05	0.797	0.71–1.57
Cesarean section												
Yes	0.26	<0.001	0.23–0.28	0.26	<0.001	0.24–0.29	1.60	<0.001	1.46–1.76	1.61	<0.001	1.47–1.77
No	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
Breastfed within 1 h:												
Yes	–	–	–	–	–	–	0.57	<0.001	0.55–0.59	0.57	<0.001	0.55–0.59
No	–	–	–	–	–	–	1.00	–	–	1.00	–	–
Personal illness control factors												
Antenatal care (4+ with any provider):												
Yes	1.07	0.009	1.02–1.12	1.07	0.008	1.02–1.12	0.90	<0.001	0.87–0.94	0.90	<0.001	0.87–0.94
No	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
Tetanus toxoid (2+ during last pregnancy):												
Yes	1.10	<0.001	1.05–1.15	1.10	<0.001	1.05–1.15	0.87	<0.001	0.83–0.90	0.87	<0.001	0.83–0.90
No	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
Skilled delivery:												
Yes	1.48	<0.001	1.40–1.56	1.50	<0.001	1.42–1.59	0.58	<0.001	0.56–0.61	0.59	<0.001	0.56–0.62
No	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–

Table 3. Continued

Socio–economic factors	All newborns, breastfeeding within 1 d								Among ever breastfed newborns, prelacteal feeds							
	OR	P	95% CI		OR	P	95% CI		OR	P	95% CI		OR	P	95% CI	
Education of mother:																
None	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
Primary	1.10	0.002	1.04	1.17	1.10	0.002	1.04	1.17	0.86	<0.001	0.82	0.91	0.86	<0.001	0.82	0.91
Secondary+	1.06	0.081	0.99	1.14	1.07	0.061	1.00	1.15	0.78	<0.001	0.73	0.83	0.78	<0.001	0.73	0.83
Marital status:																
Married/cohabiting	1.13	0.001	1.05	1.21	1.13	0.001	1.05	1.21	1.02	0.624	0.95	1.09	1.02	0.622	0.95	1.09
Not currently married/cohabiting	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
Media access:																
Yes	0.96	0.221	0.90	1.02	0.96	0.260	0.91	1.03	0.99	0.777	0.94	1.05	0.99	0.796	0.94	1.05
No	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
Household wealth status:																
Poorest quintile	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
Second quintile	1.05	0.084	0.99	1.12	1.05	0.115	0.99	1.11	0.98	0.418	0.93	1.03	0.98	0.386	0.93	1.03
Middle quintile	1.19	<0.001	1.12	1.28	1.19	<0.001	1.11	1.27	0.95	0.116	0.90	1.01	0.95	0.102	0.90	1.01
Fourth quintile	1.09	0.023	1.01	1.17	1.08	0.030	1.01	1.17	1.01	0.836	0.94	1.07	1.01	0.866	0.94	1.07
Richest quintile	1.10	0.040	1.00	1.21	1.11	0.031	1.04	1.22	1.04	0.309	0.96	1.13	1.04	0.296	0.96	1.13
Residence:																
Urban	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
Rural	0.92	0.006	0.87	0.98	0.92	0.004	0.86	0.97	1.04	0.125	0.99	1.10	1.04	0.143	0.99	1.09
Country characteristics																
GDP per capita (US$):																
High (1000+ per capita)	0.60	0.137	0.30	1.18	0.60	0.138	0.30	1.18	1.14	0.765	0.48	2.68	1.14	0.762	0.48	2.69
Low (<1000 per capita)	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
Per capita government expenditure on health at average exchange rate (US$):																
High (100+ per capita)	1.08	0.800	0.58	2.03	1.08	0.819	0.57	2.02	1.10	0.803	0.50	2.45	1.11	0.809	0.50	2.44
Low (<100 per capita)	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
No. physicians per 1000 population:																
High (0.1+)	0.62	0.052	0.38	1.00	0.62	0.054	0.38	1.01	2.26	0.009	1.22	4.17	2.26	0.009	1.22	4.18
Low (<0.1)	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
No. nurses per 1000 population:																
High (1+)	1.36	0.348	0.72	2.57	1.37	0.338	0.72	2.59	0.63	0.266	0.28	1.42	0.63	0.269	0.28	1.42
Low (<1)	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
HIV prevalence:																
High (5%+)	2.13	0.011	1.19	3.82	2.14	0.011	1.19	3.83	0.60	0.168	0.29	1.24	0.60	0.171	0.29	1.25
Low (<5%)	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
Random effects																
Country–level variance (SE):	0.147(0.055)				0.147(0.055)				0.237(0.09)				0.238(0.09)			
Log–likelihood	–28043.57				–28021.71				–34632.369				–34629.4			
AIC	56159.13				56119.41				69338.7				69336.8			
Log–likelihood ratio test (Chi–square)	715.1*				712.06*				1803.4*				1808.2*			
Total	61018				61018				59309				59309			

PNC – postnatal care, TBA – Traditional Birth Attendant, CHW – Community Health Worker

*P<0.01.

not significant (OR = 1.06, 95% CI 0.99–1.14). Women in rural areas are significantly less likely to initiate breastfeeding within a day than those in urban areas (OR = 0.92, 95% CI 0.87–0.98). Of the country–level controls in the model, higher HIV prevalence is associated with increased odds of breastfeeding within 1 day (OR = 2.13, 95% CI 1.19–3.82).

Model 2 shows that the provider of PNC is significantly associated with breastfeeding within 1 day. PNC from physicians is not associated with breastfeeding within 1 day but PNC provided by nurses/midwives/auxiliary midwives and TBA/CHW/others is associated with higher odds of breastfeeding within 1 day (nurses/midwives/aux. midwives OR = 1.39, 95% CI 1.29–1.50, TBA/CHW/others OR = 1.95, CI 1.60–2.36).

Table 3 shows that after controlling for individual and country–level variables, PNC within 1 day is not significantly associated with prelacteal feeds (OR = 1.04, 95% CI 0.98–1.09). Age is significantly associated with the outcome in the model with older women tending to have lower odds of providing prelacteal feeds to newborn while birth spacing and parity were not associated with prelacteal feeds. Newborns who had a Caesarian section delivery are significantly more likely to have PLFs (OR = 1.60, 95% CI 1.46–1.76). Contact with the health care system through ANC, tetanus toxoid vaccination and skilled delivery are significantly associated with lower odds of prelacteal feeds (see **Table 3**). For example, skilled delivery is associated with a 42% reduction in odds of prelacteal feeding (OR = 0.58, 95% CI 0.56–0.61). Education shows a clear gradient with prelacteal feeds; as the educational level of the woman increases, the odds of prelacteal feeding decreases (see **Table 3**). Of the country–level characteristics, only the density of physicians is significantly associated with prelacteal feeds in the models: higher density of physicians is associated with higher odds of prelacteal feeds (OR = 2.26, CI 1.22–4.17). In model 4 of **Table 3**, the type of provider of PNC is not associated with prelacteal feeds. Other results remain similar to model 2 of the second panel of **Table 3**.

DISCUSSION

PNC is one of the current strategies recommended for scale–up and implementation in many developing countries to improve health outcomes for newborns and mothers. While several trials and intervention studies show that PNC can improve newborn feeding patterns [30–32], this is the first study to demonstrate this association using national–level data for multiple countries in sub–Saharan Africa.

The major findings are that PNC is associated with breastfeeding within 1 day though not with prelacteal feeds. These findings are important as they suggest that PNC when delivered through customary care (as opposed to intervention and trial conditions) can be a useful strategy to improve breastfeeding (within 1 day) but not to reduce PLFs. These findings highlight the need to strengthen clinical practice so that providers of PNC can move beyond promoting timely initiation of breastfeeding to providing more emphasis on the avoidance of PLFs, which by definition would improve exclusive breastfeeding rates in these countries.

Our findings also indicate that both trained medical personal (nurses, midwives and auxiliary midwives) and untrained providers of PNC are associated with increased odds of breastfeeding within 1 day though the type of provider of PNC is not associated with PLFs. Given that all of the countries that we studied are developing countries, use of untrained persons for this type of intervention may be a useful implementation approach as the promotion of optimal newborn feeding does not require high levels of specialized training

A third important finding from this study is that, with the exception of caesarian section, contact with the formal health care system is associated with improved newborn feeding practices. This is seen in other studies eg, Nepal [27] and India [24]. This underscores the utility of the continuum of care and reinforces the need to implement around this framework. Delivery mode by caesarian section, however, is associated with poorer newborn feeding outcomes, a finding that is reflected in a number of other studies [16,24,28,36,37], even in the presence of baby–friendly policies [17].

Our study has a number of limitations. DHS data do not include any information on what procedures were done during a check and therefore cannot control for content of care. We also use cross–sectional data where PNC was not randomly assigned to individuals. As such, we are not able to provide causal linkages between PNC and the outcomes though we are able to examine associations. One of the more studied variables on breastfeeding initiation is breastfeeding within 1 hour of birth. With our data, we

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could study the association of PNC within an hour and breastfeeding within the same time period. However, we considered that a short time period of 1 hour does not provide sufficient time for PNC to be provided (given that in these settings, even PNC within 1 day is low). The literature also identifies a number of additional factors that predict early initiation of breastfeeding and PLFs which were not available for analysis. For example, intention to breastfeed [38] is an important predictor of initiation and duration of breastfeeding but was not available in DHS data. Dealing with sample weights is a challenge for analysis of this kind. Different countries contribute varying proportions of the overall sample and do not reflect the relative population size of the country. Appropriate sample weight can be constructed though the sample weights must be de–normalized. However, the appropriate sampling fraction for each country and their population sizes used to create these weights are not publicly available.

Despite these limitations, our findings are consistent with trials and intervention studies, and overall, PNC policy and practice can be further tailored to reduce PLFs rates. Further research at a country–level is needed to understand if the results of this aggregate, multi–country study are reflected within each of these countries.

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Postnatal care for newborns in Bangladesh: The importance of health–related factors and location

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Background Bangladesh achieved Millennium Development Goal 4, a two thirds reduction in under–five mortality from 1990 to 2015. However neonatal mortality remains high, and neonatal deaths now account for 62% of under–five deaths in Bangladesh. The objective of this paper is to understand which newborns in Bangladesh are receiving postnatal care (PNC), a set of interventions with the potential to reduce neonatal mortality.

Methods Using data from the Bangladesh Maternal Mortality Survey (BMMS) 2010 we conducted logistic regression analysis to understand what socio–economic and health–related factors were associated with early postnatal care (PNC) by day 2 and PNC by day 7. Key variables studied were maternal complications (during pregnancy, delivery or after delivery) and contact with the health care system (receipt of any antenatal care, place of delivery and type of delivery attendant). Using data from the BMMS 2010 and an Emergency Obstetric and Neonatal Care (EmONC) 2012 needs assessment, we also presented descriptive maps of PNC coverage overlaid with neonatal mortality rates.

Results There were several significant findings from the regression analysis. Newborns of mothers having a skilled delivery were significantly more likely to receive PNC (Day 7: OR = 2.16, 95% confidence interval (CI) 1.81, 2.58; Day 2: OR = 2.11, 95% CI 1.76). Newborns of mothers who reported a complication were also significantly more likely to receive PNC with odds ratios varying between 1.3 and 1.6 for complications at the different points along the continuum of care. Urban residence and greater wealth were also significantly associated with PNC. The maps provided visual images of wide variation in PNC coverage and indicated that districts with the highest PNC coverage, did not necessarily have the lowest neonatal mortality rates.

Conclusion Newborns of mothers who had a skilled delivery or who experienced a complication were more likely to receive PNC than newborns of mothers with a home delivery or who did not report a complication. Given that the majority of women in Bangladesh have a home delivery, strategies are needed to reach their newborns with PNC. Greater focus is also needed to reach poor women in rural areas. Engaging community health workers to conduct home PNC visits may be an interim strategy as Bangladesh strives to increase skilled delivery coverage.

The prevention of neonatal mortality has become a global priority because of the high mortality experienced by newborns and the difficulty in achieving improvements in their survival. Neonatal mortality now accounts for 45% of under–five mortality which translates to 2.8 million deaths within the first 28 days

of life. On a global level neonatal mortality rates have declined from 33 to 19 deaths per 1000 live births (from 1990 to 2015), but this 47% reduction is much less than the 58% reduction seen in deaths among post–neonatal children under–five [1]. In addition, an estimated 2.6 million stillbirths occur each year, though only a fraction of these deaths are recorded in vital registration systems [2–4]. An estimated 46% of stillbirths are intrapartum or "fresh" indicating that the fetus died after the onset of labor and perhaps could have been saved with appropriate interventions at delivery [3].

Every Newborn is an action plan focused on enabling countries to prevent neonatal deaths and stillbirths [4]. The plan emphasizes the critical periods of labor, birth and the first week of life as time points when interventions can achieve maximum impact on saving newborn lives. The plan is an extension of the United Nation's *Every Woman Every Child* movement and includes a vision, goals, strategies, and priorities for reducing newborn and stillbirth deaths. To achieve these goals, *Every Newborn* lays out key strategic objectives: 1. Improving care at birth, 2. Improving the quality and equity of maternal and newborn care, 3. Reaching every woman and newborn and achieving impact at scale, 4. Harnessing the power of parents, families and communities, and 5. Counting every newborn through measurement, program–tracking and accountability. Referral and follow–up care for low birth weight and sick newborns is also crucial given that prematurity and low birth weight are major predicators of neonatal mortality.

A continuum of services is needed to enhance newborn survival. Essential newborn care (ENC) involves care soon after birth and includes hygienic care, thermal control, support for breastfeeding and resuscitation with bag and mask, if needed [4]. Such interventions can address the main causes of neonatal mortality such as intrapartum related birth asphyxia and complications due to prematurity and low birth weight, which account for more than half of neonatal deaths [5]. Complementing essential newborn care is postnatal care (PNC) for the newborn, a package of interventions delivered after birth that includes the promotion of immediate and exclusive breastfeeding (for children less than 6 months of age), hand–washing, examination of mother and child for danger signs and appropriate referral for medical care [6]. Interventions provided as part of PNC can prevent some newborn complications such as sepsis, meningitis, pneumonia and diarrhea. PNC could be a means of providing follow–up care to newborns who were born premature and/or of low birth weight and provides an opportunity to check all newborns for illnesses that may have arisen since delivery [4].

Under–five mortality in Bangladesh has been steadily declining from 144 deaths per 1000 live births to 38 deaths per 1000 live births in the period between 1990 and 2015 [1]. Though Bangladesh laudably achieved the Millennium Development Goal (MDG) 4 target of a two–thirds reduction in under–five mortality, the burden of neonatal mortality continues to remain a concern. Neonatal mortality also declined from 63/1000 to 23/1000 during the same time period, but the magnitude of the decline was not as great as for under–five mortality. The proportion of neonatal deaths out of all under–five deaths actually increased from 44% to 62% from 1990 to 2015 [1].

Promotion of PNC has been emphasized in the National Neonatal Health Strategy and Guidelines (NNHS) of Bangladesh, and PNC is provided free of charge at government health facilities. PNC is provided both at health facilities and during home visits by community health workers in efforts to make the service accessible from the community to tertiary level. During home visits community health workers focus on the i) promotion of newborn care (early/exclusive breastfeeding, warmth, hygiene); ii) promotion of nutrition & family planning counseling to mothers; iii) providing information about danger signs of both mother and newborn; iv) Identification of danger signs in newborn and referral; v) support for breastfeeding; and vi) care of low birth weight infant (feeding, skin–to–skin contact) [7,8].

Studies in Bangladesh have found that socioeconomic factors such as education [9,10] and wealth have an influence on PNC coverage for newborns [11–16]. A study by Anwar et al. 2008 found that having at least one ANC visit [14] was associated with higher utilization of PNC, suggesting that prior contact with the health care system may be important. A qualitative study by Syed et al. 2008 found that mothers did not perceive PNC for themselves or their babies to be of much value unless they had a complication or their newborn was sick. The same study found that knowledge of maternal and newborn complications was often limited and initial care–seeking was often with a non–formal provider [17]. No quantitative studies in Bangladesh have looked at the role of complications on receipt of PNC for newborns.

The main aim of this study is to delve deeper into the question of which newborns in Bangladesh are receiving PNC by exploring not just socio–economic factors but also health–related factors, including maternal complications and contact with the health system. Our aim is to understand whether these factors, which have not been extensively studied in the literature, are associated with PNC. A secondary aim is to

use maps to descriptively present geographic variability in PNC coverage and neonatal mortality. Maps can be a useful means to pinpoint geographic areas which need more programmatic focus.

METHODS

Data and sample

Data came from the 2010 Bangladesh Maternal Mortality Survey (BMMS), a large–scale survey of 175 000 households [18]. The BMMS employed a multi–stage selection procedure designed to provide representative samples for maternal mortality at the national level and representative estimates at the national, urban/rural, divisional, and district levels for most other indicators. The BMMS Women's Long Questionnaire, which collected socio–economic and health–related information from approximately 62 000 ever–married women aged 13–49, was used in this study. We also obtained information on household wealth from the BMMS Household Questionnaire. Because the primary outcome of interest was PNC for the most recent birth, we restricted the sample to those women who had a live birth in the past six years for a total sample size of 25 014 mothers.

Data for the maps came from the BMMS 2010 as well as from a 2012 Needs Assessment of Emergency Obstetric and Newborn Care (EmONC) [19]. The BMMS 2010 provided the PNC data and population–level neonatal mortality estimates for all districts while the EmONC assessment provided data on facility–level neonatal mortality for 24 of the 64 districts of Bangladesh.

This study was reviewed by the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill and was exempted from needing ethics review approval because of the secondary nature of the analysis.

Descriptive and regression analyses

Outcomes

We calculated simple weighted descriptive statistics and chi–square analyses on all predictor and demographic variables, comparing women who reported receiving PNC on or before day 7 and on or before day 2 (early PNC) to those who did not. The sample for early PNC is a subset of the larger PNC on or before day 7 sample. Early PNC was defined as within a day for facility births and within two days for non–facility births. The WHO indicates that PNC should be given to newborns within 24 hours for both facility births and as soon as possible for non–facility births [6,20]. We therefore included day 2 as relevant for early PNC for non–facility births.

Key independent variables

Our key predictor variables were focused on access to maternal health services and the presence of complications. In terms of maternal health services we included receipt of ANC, type of delivery attendant (Skilled Birth Attendant (SBA) or non–SBA), place of delivery (facility vs non–facility). A SBA was defined according to the World Health Organization's definition as "an accredited health professional – such as a midwife, doctor or nurse – who has been educated and trained to proficiency in the skills needed to manage normal (uncomplicated) pregnancies, childbirth and the immediate postnatal period, and in the identification, management and referral of complications in women and newborns" [21]. We, thus, defined a SBA as an accredited doctor, nurse or midwife. All others including traditional birth attendants (TBAs) were defined as non–SBAs. We looked at both the type of delivery attendant and place of delivery because Bangladesh promotes a strategy of home deliveries by SBAs when facility delivery is not feasible [22,23]. Complications reported by the mother at labor, delivery and after delivery were also key measures in our analysis. Though the BMMS included questions on timing of complication, questions on specific types of complications were not included. We were not able to include four or more ANC visits and low birth weight in our analysis because of a large amount of missing data, and data on neonatal complications were not available.

Regression analysis

We performed weighted logistic regression models predicting receipt of the PNC outcomes, controlling for maternal age, parity, highest level of education, urban residence, marital status, and wealth quintile.

The wealth index was constructed from data on ownership of household items including bathroom facilities, roofing, and flooring. Each asset was assigned a weight (factor score) generated through principle components analysis. Each household's scores were then summed; individuals were ranked according to the total score of the household in which they resided [18]). All analyses were performed using Stata v. 14.

Maps and chi–square comparisons

Descriptive maps of PNC by day 7 and early PNC were interposed with data on population–level neonatal mortality and facility–level neonatal mortality to present subnational level variation in PNC coverage and neonatal mortality. We also performed χ^2 analyses of the key independent variables and PNC with neonatal mortality. Studying associations between PNC and neonatal mortality, however, has its limitations. The data do not allow for a determination of whether or not deaths on the first day of life occurred to newborns before they were even eligible for PNC [9]. For example, there could be some left censoring in that some newborns might have died within minutes of birth before they could have received a PNC check, but the data does not disaggregate deaths on the first day into hours or minutes.

RESULTS

Table 1 reports sample characteristics for PNC by day 7, while **Table 2** does the same for early PNC. Given that early PNC is a subset of the PNC by day 7 outcome, the number of women who received early PNC is smaller than PNC by day 7 (7461 vs 8258). Thirty–three percent of respondents reported receipt of PNC by day 7, while 30% reported early PNC. For every characteristic except marital status, there were differences between women receiving PNC by day 7 and not receiving PNC by day 7. For example, women who reported contact with the health system in terms of ANC, facility delivery or delivery with a SBA were more likely to report PNC by day 7. Women who reported a complication during pregnancy, delivery or after delivery as well as urban, wealthier and more educated were also more likely to indicate their newborns received PNC by day 7. Results were similar when comparing women receiving early PNC to those who did not (**Table 2**).

Table 3 shows results from the logistic regressions of PNC by day 7 and by day 2. Confirming some of the findings shown in **Tables 1** and **2**, controlling for maternal demographic characteristics, having had a skilled delivery significantly increased the odds of reporting PNC by day 7 and by day 2 by over 2.1 times (odds ratio (OR)=2.16, 95% confidence interval (CI) 1.81, 2.58; OR=2.11, 95% CI 1.76, 2.54, respectively). Having had a home delivery significantly decreased the likelihood of PNC by about 85% (OR=0.15, 95% CI 0.12, 0.18; OR=0.14, 95% CI 0.12, 0.17, respectively). Reporting complications during pregnancy, delivery and after delivery significantly increased the odds of reporting PNC by between 1.3 and 1.6 times. Urban residence significantly increased the odds of reporting PNC by day 7 or by day 2 by about 1.4 times (OR=1.38, 95% CI 1.22, 1.55; OR=1.40, 95% CI 1.23, 1.59, respectively). Being in the top three wealth quintiles also increased the odds of reporting PNC by day 7 and by day 2 by between 1.5 and 2.3 times.

Figures 1 and **2** present descriptive maps of PNC coverage interposed with population–level neonatal mortality (**Figure 1**) and facility–level neonatal mortality (**Figure 2**). Overall, there is wide variation in the PNC (from 4% to 64%) and population–level neonatal mortality rates (from 1.6 per 1000 to 96.2 per 1000) within Bangladesh. Districts with the lowest neonatal mortality do not always have the highest PNC coverage and vice versa. Chi–square statistics for key independent variables and PNC with neonatal mortality indicate significantly higher mortality for newborns receiving PNC by day 2 and for newborns of mothers having a complication and a skilled delivery. These results are presented in **Figure 3**.

DISCUSSION

PNC is a package of interventions intended for all newborns and has both a preventative focus and curative focus. In our study of PNC in Bangladesh we find that newborns whose mothers had a facility delivery or who had a complication were likely to have a PNC check than newborns of mothers who delivered at home or did not have a complication. Given that 79% of women in our sample had a home birth, efforts are needed to ensure all newborns are reached.

PNC for newborns may not always be perceived to be necessary by mothers and their families in Bangladesh [17]), unless there is a complication or the newborn appears sick. Education of families on the im

Table 1. Sample characteristics by postnatal care on or before day 7 (n = 25 014)

Characteristic	No PNC by day 7		PNC by day 7		
	n	(%)	n	(%)	P
Total	16 756	67.0	8258	33.0	
Predictor variables					
Delivery:					
– Unskilled	15 307	93.3	3489	46.0	
– Skilled	1449	6.7	4769	54.0	<0.001
Home delivery:					
– No	1078	5.2	4622	52.7	
– Yes	15 678	94.8	3636	47.3	<0.001
Any antenatal care (ANC):					
– No	6615	40.5	1135	14.8	
– Yes	10 141	59.5	7123	85.2	<0.001
Reported complications during pregnancy:					
– No	11 190	66.5	4158	49.7	
– Yes	5566	33.5	4100	50.3	<0.001
Reported complications during delivery:					
– No	13 099	78.0	5209	62.5	
– Yes	3657	22.0	3049	37.5	<0.001
Reported complications after delivery:					
– No	13 818	82.8	6270	75.9	
– Yes	2938	17.2	1988	24.1	<0.001
Demographic characteristics					
Maternal age (years):					
– 13 to 19	1950	11.7	914	11.5	
– 20 to 24	5363	32.6	2938	36.2	
– 25 to 29	4782	28.3	2329	27.9	
– 30 to 34	2677	15.9	1268	14.8	
– 35 to 39	1324	7.6	574	6.7	
– 40 to 44	485	2.9	179	2.1	
– 45 to 49	175	1.0	56	0.7	<0.001
Highest level of education (class):					
– None	4964	30.2	1269	16.0	
– 1 to 5	5658	33.3	2031	25.5	
– 6 to 8	3402	20.7	1789	22.6	
– 9+	2732	15.8	3169	35.9	<0.001
Urban residence:					
– No	10 773	81.9	3955	64.4	
– Yes	5983	18.1	4303	35.6	<0.001
Religion:					
– Islam	15 349	92.4	7334	89.8	
– Hindu/other	1407	7.6	924	10.2	<0.001
Marital status:					
– Currently not married	324	1.8	127	1.5	
– Currently married	16 432	98.2	8131	98.5	0.199
Wealth index quintile:					
– Poorest	4234	26.4	790	10.8	
– Poorer	3702	22.8	964	12.5	
– Middle	3522	21.5	1384	18.0	
– Richer	3047	17.7	1878	22.7	
– Richest	2251	11.6	3242	35.9	<0.001

portance of PNC as a preventative service can lead to improvements in newborn health. Early treatment for illnesses such as pneumonia is crucial, and PNC offers an opportunity for health workers to look for signs of illnesses which may be missed by family members.

Traditional practices may prevent many mothers from leaving their homes for up to 40 days after delivery [24,25]. During this period of isolation, mothers are considered to be in a state of impurity and vulnerability to evil spirits [25]. Mothers often sleep on thin mats on the floor with their newborns to minimize the spread of pollution to others and protect themselves from spiritual attacks [16,25]. Husbands

Table 2. Sample characteristics by postnatal care on or before day 2 (early PNC, n = 25 014)

Characteristic	No PNC by day 2		PNC by day 2		
	n	%	n	%	P
Total	17 553	70.2	7461	29.8	
Predictor variables					
Delivery:					
– Unskilled	15 898	92.6	2898	42.6	
– Skilled	1655	7.4	4563	57.4	<0.001
Home delivery:					
– No	1247	5.7	4453	56.4	
– Yes	16 306	94.3	3008	43.6	<0.001
Any antenatal care (ANC):					
– No	6786	39.7	964	14.0	
– Yes	10 767	60.3	6497	86.0	
Reported complications during pregnancy:					
– No	11 584	65.7	3764	49.8	
– Yes	5969	34.3	3697	50.2	<0.001
Reported complications during delivery:					
– No	13 637	77.5	4671	61.9	
– Yes	3916	22.5	2790	38.1	<0.001
Reported complications after delivery:					
– No	14 402	82.4	5686	76.2	
– Yes	3151	17.6	1775	23.8	<0.001
Demographic characteristics					
Maternal age (years):					
– 13 to 19	2036	11.7	828	11.5	
– 20 to 24	5646	32.7	2655	36.4	
– 25 to 29	4999	28.3	2112	28.0	
– 30 to 34	2816	16.0	1129	14.5	
– 35 to 39	1371	7.5	527	6.9	
– 40 to 44	502	2.8	162	2.1	
– 45 to 49	183	1.0	48	0.7	<0.001
Highest level of education (class):					
– None	5122	29.8	1111	15.5	
– 1 to 5	5924	33.3	1765	24.7	
– 6 to 8	3567	20.8	1624	22.6	
– 9+	2940	16.1	2961	37.2	<0.001
Urban residence:					
– No	11 226	81.6	3502	63.3	
– Yes	6327	18.4	3959	36.7	<0.001
Religion:					
– Islam	16 072	92.3	6611	89.6	
– Hindu/other	1481	7.7	850	10.4	<0.001
Marital status:					
– Currently not married	340	1.8	111	1.5	
– Currently married	17 213	98.2	7350	98.5	0.2028
Wealth index quintile:					
– Poorest	4357	26.0	667	10.1	
– Poorer	3835	22.6	831	11.9	
– Middle	3697	21.6	1209	17.5	
– Richer	3213	17.9	1712	22.9	
– Richest	2451	12.0	3042	37.5	<0.001

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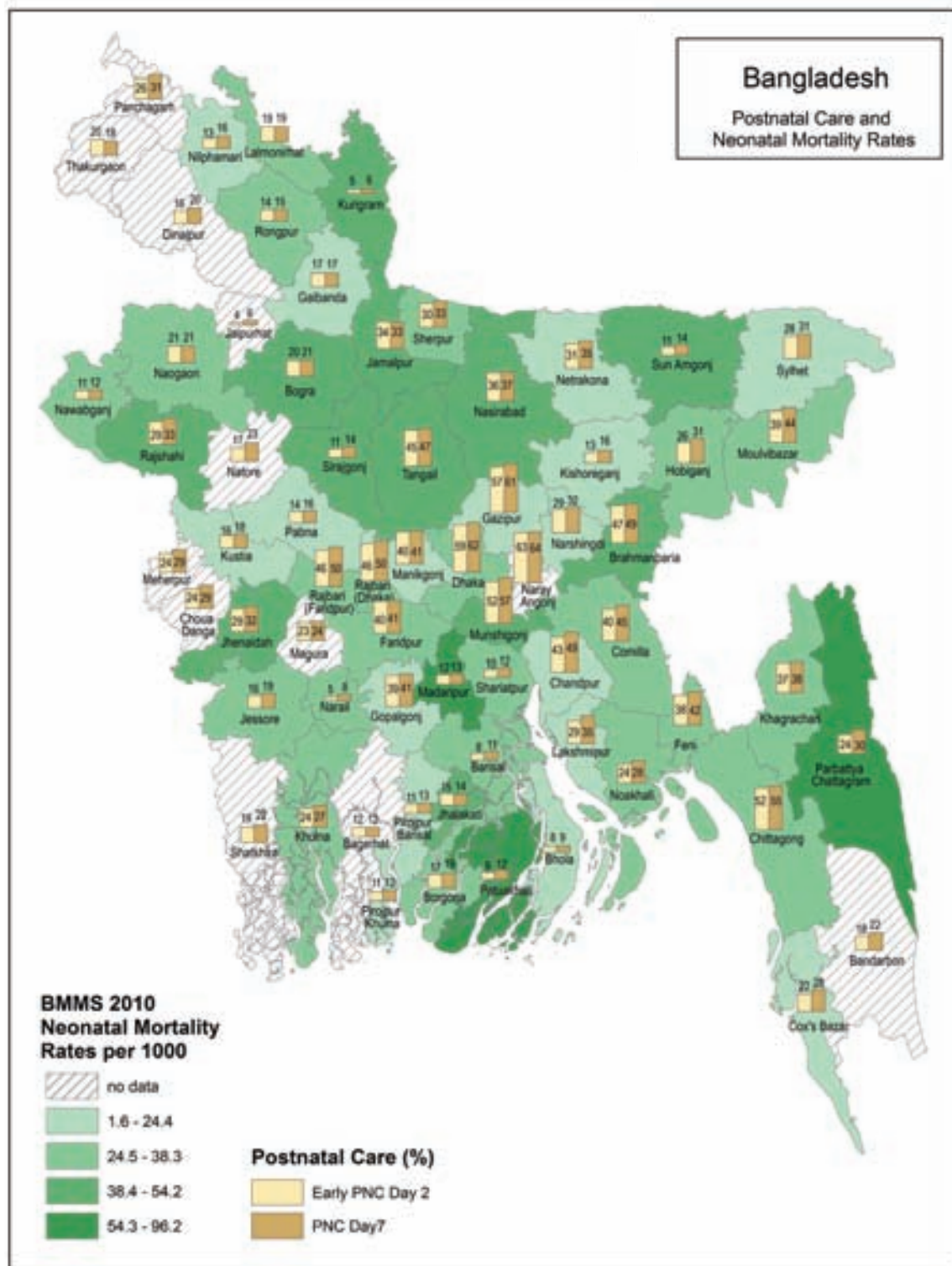
Figure 1. Postnatal care (PNC) and population–level neonatal mortality by district.

and mothers–in–law may also serve as gatekeepers to ensure minimal contact with outsiders during this period [25–28]. In light of these cultural issues, training community health workers to provide PNC for mothers and newborns at home, has surfaced as an interim solution to increasing the coverage of PNC [24,29,30]. Community health workers have the ability to gain the trust and support of mothers, fathers and mothers–in–law. They can engage these individuals on discussions concerning newborn care and any harmful traditional practices. For example, if newborns are sleeping on thin mats, community health workers can educate families on the risks of hypothermia. Studies conducted in rural Bangladesh have

Figure 2. Postnatal care (PNC) and facility–level neonatal mortality by district.

documented that community health workers are capable of correctly identifying sick newborns with a 6–sign or 7–sign clinical algorithm during their routine surveillance of newborns at home [28,31]. Home visits from community health workers by day 2 have been shown to reduce neonatal mortality [32]. Home visits have also been shown to be an effective means to assist mothers in overcoming breastfeeding problems [33].

In addition to identifying methods to reach more individual newborns, it is also important to study PNC coverage at a subnational level to enable countries to address geographic inequities. In Bangladesh there

Table 3. Logistic regressions of postnatal care by day 7 and by day 2 on predictor variables (n=25 014)

	PNC by day 7			PNC by day 2		
Characteristic	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Predictor variables						
Skilled delivery	2.16	1.81–2.58	<0.001	2.11	1.76–2.54	<0.001
Home delivery	0.15	0.12–0.18	<0.001	0.14	0.12–0.17	<0.001
Any antenatal care (ANC)	1.74	1.58–1.92	<0.001	1.71	1.54–1.89	<0.001
Complications during pregnancy	1.60	1.45–1.73	<0.001	1.49	1.36–1.64	<0.001
Complications at delivery	1.48	1.34–1.63	<0.001	1.53	1.38–1.69	<0.001
Complications after delivery	1.36	1.22–1.51	<0.001	1.32	1.18–1.48	<0.001
Demographic characteristics						
Maternal age (years):						
– 13 to 19	1.00					
– 20 to 24	1.12	0.98–1.27	0.110	1.10	0.96–1.27	0.172
– 25 to 29	1.07	0.91–1.25	0.431	1.06	0.90–1.26	0.478
– 30 to 34	1.02	0.84–1.23	0.856	0.98	0.81–1.19	0.841
– to 39	1.11	0.89–1.39	0.362	1.18	0.93–1.50	0.184
– 40 to 44	1.13	0.84–1.52	0.403	1.19	0.87–1.61	0.272
– to 49	1.52	1.01–2.29	0.047	1.52	0.98–2.37	0.060
Parity:						
– 1	1.00					
– 2–3	0.91	0.82–1.01	0.069	0.92	0.82–1.02	0.111
– 4+	0.94	0.80–1.11	0.450	0.91	0.76–1.08	0.278
Highest level of education (class):						
– None	1.00					
– 1 to 5	1.10	0.98–1.23	0.091	1.06	0.94–1.20	0.372
– 6 to 8	1.08	0.94–1.23	0.277	1.05	0.91–1.22	0.492
– 9+	1.14	0.99–1.31	0.073	1.11	0.95–1.29	0.174
Urban residence:						
– No	1.00					
– Yes	1.38	1.22–1.55	<0.001	1.40	1.23–1.59	<0.001
Religion:						
– Islam	1.00					
– Hindu/other	1.09	0.93–1.28	0.284	1.07	0.91–1.27	0.412
Marital status:						
– Currently not married	1.00					
– Currently married	1.04	0.77–1.41	0.791	1.04	0.76–1.44	0.793
Wealth index quintile:						
– Poorest	1.00					
– Poorer	1.15	1.00–1.32	0.058	1.14	0.98–1.32	0.090
– Middle	1.47	1.29–1.68	<0.001	1.46	1.27–1.69	<0.001
– Richer	1.65	1.42–1.91	<0.001	1.68	1.43–1.97	<0.001
– Richest	2.32	1.97–2.74	<0.001	2.35	1.97–2.80	<0.001
Constant	0.45	0.31–0.66	<0.001	0.40	0.27–0.60	<0.001
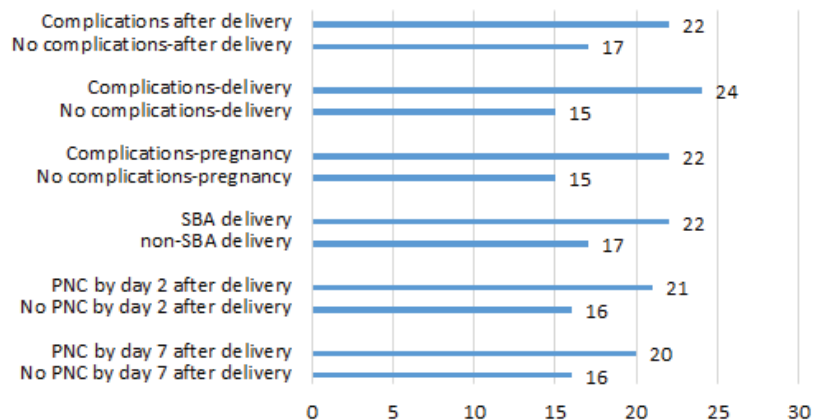
Figure 3. Bivariate associations between selection variables and neonatal mortality (per 1000). Note: All comparisons are significant at P<0.05 or P<0.0001 except for PNC by Day 7 (P=0.0635). PNC – postnatal care, SBA – skilled birth attendant.

is wide variation in PNC coverage. Understanding why some districts have lower coverage than others can help inform intervention strategies. Traditional practices such as seclusion of the mother and newborn may be more prevalent in some districts than others, and thus engagement with communities on the importance of PNC (whether in a facility or in the home) may be particularly helpful.

Our maps also revealed that districts with the highest PNC coverage did not necessarily have the lowest neonatal mortality and vice versa. We further explain this finding through bivariate comparisons of our key independent variables and PNC with neonatal mortality. The findings indicated significantly higher neonatal mortality when there is a PNC by day 2 check, maternal complication and delivery with a skilled birth attendant. Families in Bangladesh seem to view PNC as a service needed only when there is a problem with the mother or newborn. According to the BMMS 2010, 56% of mothers whose newborns did not receive PNC, indicated the reason was that the service was "not needed" [18]. Unfortunately, we lacked data on newborn complications, prematurity and low birth weight.

There are several limitations to this study including our inability to include certain measures including neonatal complications, four or more ANC visits and birthweight. Though we looked at bivariate associations of PNC with neonatal mortality, there could be some left censoring of the data in that some newborns could have died before they were eligible for PNC [9]. Another limitation is the measurement of PNC itself as some women may not realize their newborn is receiving a check. Direct questions on PNC without probes, as was used in the BMMS, may lead to an underestimation of coverage [34]. The BMMS did not include questions on content or quality of the PNC check, and future research is needed to develop measures on both content and quality of PNC.

Based on the findings of this study, several programmatic recommendations can be made. Both formal health workers and community health workers should provide PNC, a service essential for both for its preventative and curative elements. Particular efforts are needed to reach rural and poor women. Bangladesh has already taken relevant steps to reduce neonatal mortality by developing a National Newborn Health Strategy, which includes PNC provided by community health workers as a national health sector program approach [35]. Important considerations for such an approach are ensuring community health workers have the proper training, supplies and supervision to conduct their work. Community health workers also need to be notified of both facility and home births so that more newborns can be reached [36]. In addition to supporting community health workers, efforts are needed to increase the quality of PNC services in health facilities and to educate families on recognizing the value of PNC for seemingly healthy newborns as well as for sick newborns.

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Does health facility service environment matter for the receipt of essential newborn care? Linking health facility and household survey data in Malawi

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Background Health facility service environment is an important factor for newborns survival and well–being in general and in particular in high mortality settings such as Malawi where despite high coverage of essential interventions, neonatal mortality remains high. The aim of this study is to assess whether the quality of the health service environment at birth is associated with quality of care received by the newborn.

Methods We used data from the Malawi Millennium Development Goals Endline household survey conducted as part of MICS survey program and Service Provision Assessment Survey carried out in 2014. The analysis is based on 6218 facility births that occurred during the past 2 years. Descriptive statistics, bivariate and multivariate random effect models are used to assess the association of health facility service readiness score for normal deliveries and newborn care with newborns receiving appropriate newborn care, defined for this analysis as receiving 5 out of 6 recommended interventions during the first 2 days after birth.

Results Newborns in districts with top facility service readiness score have 1.5 higher odds of receiving appropriate newborn care (adjusted odds ratio (aOR) = 1.52, 95% confidence interval CI = 1.19–1.95, *P* = 0.001), as compared to newborns in districts with a lower facility score after adjusting for potential confounders. Newborns in the Northern region were two times more likely to receive 5 newborn care interventions as compared to newborns in the Southern region (aOR = 2.06, 95% CI = 1.50–2.83, *P* < 0.001). Living in urban or rural areas did not have an impact on receiving appropriate newborn care.

Conclusions There is need to increase the level of service readiness across all facilities, so that all newborns irrespective of the health facility, district or region of delivery are able to receive all recommended essential interventions. Investments in health systems in Malawi should concentrate on increasing training and availability of health staff in facilities that offer normal delivery and newborn care services at all levels in the country.

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Recent evidence estimates that care around the time of birth including having a skilled attendant at birth, emergency obstetric care, immediate care for newborns, and newborn resuscitation could prevent 1.5 million maternal and newborn deaths and stillbirths by 2025 [1]. The days and weeks around childbirth and immediate postnatal period – are the most vulnerable for both mothers and newborns. Most maternal and infant deaths occur during this time [2].

Care during the time of labour, child birth and early, postnatal care (PNC), presents a unique opportunity to set both mothers and babies on a good start. Postnatal care also provides the delivery platform for care of the newborn, including the promotion of preventive practices and detection of any complications. Care of the normal newborn includes early initiation of (exclusive) breastfeeding, prevention of hypothermia, clean postnatal care practices and appropriate cord care [3]. Close observation for 24 hours and at least three additional postnatal contacts is recommended for all mothers and newborns to establish good caregiving practices and detect any life–threatening conditions [4]. However, for improved effectiveness, newborn care interventions in the postnatal period should be delivered as a package. Every Newborn Action Plan launched in 2014 to end preventable newborn deaths envisages each country to ensure 90% of all births receive quality care improve PNC coverage at least by 20% by 2020 and 90% by 2030. PNC is also a key indicator for EWEC monitoring framework which will facilitate monitoring of SDG targets by 2030 [3].

Addressing newborns' health is a priority in Malawi as in many countries in sub–Saharan Africa. In 2015, newborns in Malawi accounted for 34% of all under–5 deaths, an increase from 2000 when newborns accounted for 20% of under–five deaths [5]. This increase in proportion of newborn deaths in overall under–five deaths speaks about the effect of immunization and reduction of diarrhoea and pneumonia related mortality. Malawi is one the few counties in sub–Saharan Africa which has reached the MDG goal 4 by reducing under–five deaths by 63% between 1990 and 2015. During the same period, the country also reduced its maternal mortality ratio by over one–third (34%) and witnessed a substantial increase in the rate of institutional deliveries; from 55% in 2000 to 91% in 2016 [6]. However, between 1990 and 2015, neonatal deaths have declined by only 36% (6). Additionally, recent data shows wide regional variations with regards to perinatal mortality rate. In 2016, the Central region had a perinatal mortality rate of 42 per 1000 pregnancies compared to 29 per 1000 in the Southern region [7]. The slower decline in newborn mortality relative to under–5 mortality in Malawi calls for a redoubling of efforts, including attention to premature babies and care for small and sick babies [8].

In Malawi, health care services are provided by three agencies; Government through the Ministry of Health (MoH) provides about 60%; the Christian Health Association of Malawi (CHAM) is responsible for about 39% plus a small contribution from the private–for profit health sector [9]. Attention to newborn health intensified after 2005 as the Government of Malawi integrated newborn survival and implemented the Essential Health Package and developed a multi–year national initiative (2005–2015), the 'Road Map' for Accelerating Reduction of Maternal and Newborn Mortality and Morbidity in Malawi [10]. Malawi Newborn Action Plan was developed and launched in 2015 and the country recently committed to WHO–UNICEF's network for Improving Quality of Care for Maternal, Newborn and Child Health. Ministry of Health engaged NSO to conduct partner resource mapping exercise and results showed variations in terms of support on MNCH interventions including newborns. There was more concentration mostly on maternal issue than new born issues leading to verticalization in the implementation on newborn care either by partners or districts. As identified by health authorities in the country, challenges in Malawi remain both acute and complex with projections on human resources. To ensure adequate staffing at health facilities, in 2012 the Government implemented an "Emergency Human Resource" program for re–engagement and redeployment of staff [11]. This has not been implemented fully and the health sector strategic plan 2 (2017–2022) is carrying on this work. Still, at current output levels, it will take many years to come anywhere near the numbers of health staff needed to provide minimum standards of service delivery [12].

The quality and availability of health services that are within reach to mothers and newborns, the service environment, plays a major role in the provision of good care. The relationship between health services and population outcomes is an important area of public health research that requires bringing together data on health outcomes and the relevant health service environment [13]. However, as newborn health is relatively new on the global agenda, data on the service environment for this vulnerable group is still scarce [14]. Malawi presents a great opportunity to explore the convergence of complementary data on health facilities and population–based data on this topic as it is one of the few countries with census facility data and household survey data within a range of close years readily and publicly available for analysis.

An important additional consideration in many low–income settings is the distance to health facilities, particularly in rural areas as roads may not be optimal and vehicles for transport are rarely available.

Distance to delivery care and the level of care provided are important determinants of facility delivery [15] and thus of the well–being of mothers and babies. Recent studies in sub–Saharan Africa show a significant variation in receiving postnatal care. Across communities in Nigeria and Uganda [16] studies have

found that distance to health facilities as well as socio economic factors are important determinants for accessing services [17,18]. Recent geospatial analysis have also identified that targeted interventions at the district level are essential to strengthen maternal health programmes [19,20]. This study investigates if living in a district with health facilities that are ready to provide a high level of normal delivery and newborn care is associated with receiving a package of essential newborn care interventions during the first two days after birth.

METHODS

Data

Two main sources of data have been used for this analysis: the Malawi MDG Endline Survey 2014 – MES conducted as part of the UNICEF supported MICS survey program [21] which is a population–based household survey representative at the national and district level, and the Malawi Service Provision Assessment 2013–2014 – MSPA 2014 [22], which is based on a census of health facilities in the country. To determine population densities across districts, we used census data from the Malawi 2008 census as 2013–14 projections were not available at the time of the analysis [23].

Population based data

The Malawi MDG Endline Survey (MES) was carried out in 2013–14 by Malawi National Statistical Office as part of the global Multiple Indicator Cluster Survey (MICS) programme. Technical support was provided by the United Nations Children's Fund (UNICEF). The sample for the MES 2014 was designed to provide estimates for a large number of indicators at the national level; for urban and rural areas; the three regions (Northern Region, Central Region and Southern Region); and the 27 districts of Malawi excluding the island of Likoma due to logistical challenges. The sample was stratified by district with the aim of obtaining representative estimates at each district level. Within each district, the sample was further stratified by urban–rural, before a two stage cluster sampling was implemented. Within each stratum, a specified number of census enumeration areas were selected systematically with probability proportional to size [21]. All the information obtained from respondents remains strictly confidential and anonymous. Although GPS coordinates of each sample cluster was collected, this information was not collected of respondents' household.

In the MES 2014, a total of 24 230 women aged 15–49 years were interviewed between November 2013 and April 2014. Of the interviewed women, 31% had a live birth in the past two years, for a total of 7490 reported live births. Of these, 89% were born in health facilities (6661 live births). In the survey, women were asked questions about interventions related to maternal and newborn care that mothers and their newborns received immediately after birth and in the following few weeks. These questions include a number of critical interventions such as thermal care, feeding practices like early initiation of breastfeeding, weighing of the baby and more that are recommended to occur during the postnatal period to ensure the well–being of the baby [2]. Of the 6661 facility–based births in the last two years reported in the household survey, 6218 had complete data on all variables of newborn care and were included in the analysis.

Health facility data

The Malawi Service Provision Assessment MSPA 2014 was implemented by the Malawi Ministry of Health. ICF International provided technical assistance through the MEASURE DHS program, which is funded by USAID and is designed to assist countries in collecting data to monitor and evaluate population, health, and nutrition programmes [22]. The MSPA 2014 is considered a census of facilities in the country as it covers all of Malawi's health facilities including public and semi–public facilities of all levels, CHAM as well as major private facilities [22]. The survey assesses whether components considered essential for quality service delivery are present and functioning [22]. Data also includes precise location using GPS of all facilities in the country.

Of the 977 health facilities in Malawi, 528 (54%) were recorded as providing normal delivery and newborn care services and were included in the study. For this analysis, data from the MSPA 2014 facility and providers data sets were used. These modules collected information on basic emergency and neonatal services in key domains including: staff and training, equipment, and key medicines and commodities

relevant during delivery and to provide care for the newborn. Variables about health facility services were ascertained through observation and health facility staff interviews, in the facility and providers data set of the MSPA 2014 [22]. No missing data was observed for the variables included from the MSPA 2014 facility and provider data sets in this analysis.

Definition of outcome and exposure

Outcome: Appropriate newborn care

In 2013, WHO released the Postnatal Care for Mother and Newborn guidelines which provided a list of recommendations for the care of the mother and newborn in the postnatal period [2]. The specific recommendations for the newborn included assessment of the baby, exclusive breastfeeding, cord care and thermal care interventions. We recognize that the scope of newborn care in the postnatal period is broad and encompasses a range of interventions. But, for the purposes of this analysis, appropriate newborn care is defined as co–coverage of essential interventions received by the newborn in the period immediately after birth and up to 2 days after birth for which data was available in the Malawi MES 2014 survey. Thus, a newborn was considered to have received appropriate newborn care if he/she received 5 out of 6 of the following interventions: 1) being weighed after birth, 2) being put to the breast during the first hour after birth, 3) not having received pre–lacteal feeds, 4) being wiped/dried after birth, 5) being bathed not before 6 hours after birth, 6) having received a postnatal check within 2 days following birth. The interventions for immediate care for newborns selected in this analysis were also consistent with the recommendations in the Every Newborn Action Plan (ENAP), which at its onset provided evidence of the effectiveness of these interventions for improving newborn survival [1]. The "appropriate newborn care" score was calculated using equal weights for each of the six components (Table S1a in **Online Supplementary Document**). The present analysis focused only on normal newborns and did not include premature, sick babies requiring additional interventions.

Exposure: Facility level readiness score

The quality of delivery and newborn care services offered in health facilities are characterized by calculating the service readiness score for "normal delivery and newborn care" based on the Service Availability and Readiness Assessment (SARA)."– *Reference Manual* [24]. The score includes three domains: 1) staff and training: having guidelines for integrated management of pregnancy and childbirth (IMPAC) and having staff trained in IMPAC. IMPAC was selected as the Malawi service provision assessment reports on IMPAC as the guidelines for facilities offering normal delivery service [22], 2) equipment and commodities (observed and functioning) and 3) medication and supplies availability. A total of 20 tracer indicators were included in the construction of the score (Table S1b in **Online Supplementary Document**), covering the 19 SARA tracer indicators plus having an infant scale given its relevance to the outcome under investigation. Facility specific scores ranged from 19 to 100. These scores were then aggregated at the district level using weighted average and the final scores were not stratified by the type of facility. To account for facility utilization, district level scores were weighed by the number of outpatient clients in each facility. District level service readiness scores ranged from 56 to 80 with a mean of 67.1. For ease of interpretation, these were then categorized into terciles based on their mean value: bottom (55.7–62), middle (62–70) and top (70–79.5) (**Figure 1**).

Method of analysis

To investigate the association between appropriate newborn care for newborns and district average facility service readiness score, the two data sources were linked using the administrative boundary linking method. This approach consists of linking the two data sets at a level at which both are representative [25]. Thus, following this method, facility data were aggregated at the district level and then merged with the individual level household survey data set for subsequent analysis. Recent analysis linked health facility and household survey using this same method for the analysis of availability of improved water and sanitation in the childbirth environment in 58 countries [26]. The study undertook an ecological type of analysis where facility births in a particular district were assigned their respective district average health facility score. Thus, each of the 6218 facility births from the individual data set included in the analysis was assigned a district average health facility score value according to their district location.

Bivariate regression analyses of potential confounders related to household, mother, delivery and infant (Table S1a in **Online Supplementary Document**) were analysed for association with the primary out
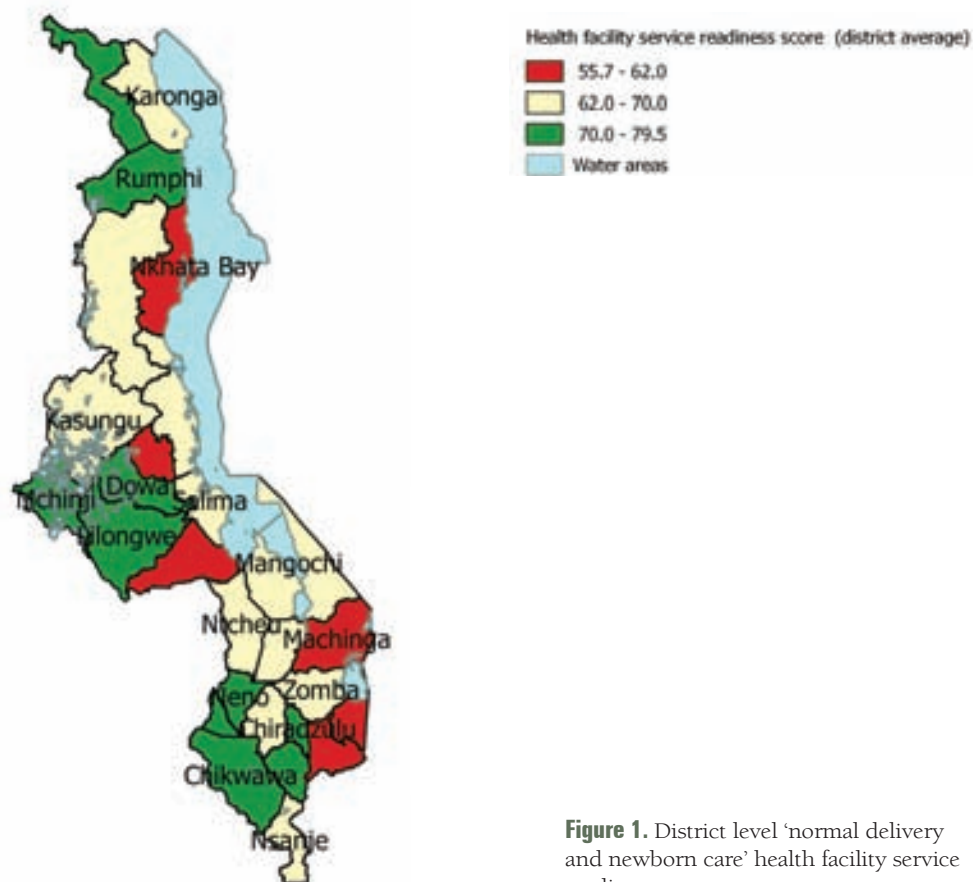
Figure 1. District level 'normal delivery and newborn care' health facility service readiness score.

come of appropriate newborn care. Variables found to be significant in the bivariate analysis were selected for inclusion in the final model. A random effect multiple logistic model was used to assess the association between the variables of interest. This implies that levels of 'appropriate newborn care' in neighbouring districts are unrelated after adjusting for other variables in the model. This modelling technique was used given the structure of the data and to account for the effects of clustering. All variables kept in the model were checked for multicollinearity by assessing variance inflation factor. Analysis was conducted in Stata 14.0 [27] and maps were produced in QGIS desktop 2.14.0. [28].

Ethical approvals

All data are publicly available and therefore no ethics approval was required for this analysis. Ethical approval for data collection was the responsibility of data collectors.

RESULTS

Descriptive analysis

Table S2 in **Online Supplementary Document** presents the distribution of health facilities with service–readiness score (70 or above) in the top category in each domain. This descriptive analysis reveals that 52% of the facilities in urban areas have a service readiness score of 70 or higher, in contrast to rural areas where only 32% of the facilities recorded high scores. The results are further disaggregated by regions and districts. The domain with the lowest performance is staff and training. Across districts, there is a wide range in the proportion of facilities with a high score on this domain (range: 0–55%; mean 21.7%). For the equipment and supplies domain, the range is 25.2 to 77.6% (mean 46.7%) of facilities with scores in the top category. For the medicines and commodities domain, the range is 20.0 to 81.8% (mean 54.5%) with score 70 or higher. Across all districts, 35.3% of facilities (range 16.8 to 66.8%) have a service readiness score of 70% or higher. **Figure 1** presents the mean district health facility score.

At the individual level, of the 6218 facility births, 37% were in districts in which the average facility service readiness score was above 70%. Of all newborns included in the analysis, 88% were located in rural areas and 12% in urban areas, 14% were born to mothers younger than 20 years old, for 82% their mothers had either no education (11%) or only primary education (71%). Of the 6218 births, 86% were delivered in public health facilities (**Table 1**).

Bivariate analysis

Analysis of essential newborn care interventions across regions found that the Southern region presents lower coverage of newborns receiving all 6 newborn care interventions (37.1% CI = 34.4–39.9) (Table S3

Table 1. Distribution of study population characteristics – live births in facilities in the past 2 years and crude associations with outcome (N = 6218)

Indicators	Total n (%)	Prevalence >5 5 newborn care interventions (%)	Unadjusted OR (95% CI)	P
Health facility readiness score (district average):				<0.001
Bottom (55.7–62)	2117 (34)	1714 .0)	1	
Middle (62–70)	1813 (29)	1570 (86.6)	1.52 (1.21–1.91)	<0.001
Top (70–79.5)	2288 (37)	1994 (87.2)	1.60 (1.25–2.03)	<0.001
Place of residence:				
Urban	745 (12)	663 (88.9)	1	
Rural	5473 (88)	4615 (84.3)	0.67 (0.50–0.90)	<0.001
Region:				
Southern	3018 (48)	2457(81)	1	
Central	2467 (40)	2165 (87.7)	1.63 (1.32–2.02)	<0.001
Northern	733 (12)	656 (89.5)	1.95 (1.32–2.90)	<0.001
Mother's age at birth (years):				
<20	850 (14)	707 3.3)	1	
20–34	4617 (74)	3841 (85.1)	1.14 (0.85–.152)	0.374
35–49	852 (14)	729 (85.6)	1.18 (0.84–1.68)	0.329
Mother's education:				
None	664 (11)	542 1.6)	1	
Primary	4387 (71)	3722 (84.8)	1.27 (0.97–1.65)	0.080
Secondary or higher	1168 (19)	1014 (86.9)	1.49 (1.05–2.12)	0.025
Household wealth index:				
Poorest	1464 (24)	1203 .2)	1	
Second	1389 (22)	1176 (84.7)	1.19 (0.91–1.58)	0.200
Middle	1290 (21)	1093 (84.7)	1.20 (0.88–1.64)	0.240
Fourth	1059 (17)	911 (86.1)	1.34 (0.96–1.86)	0.081
Richest	1017 (16)	894 (87.9)	1.58 (1.12–2.22)	0.008
Type of health facility:				
Public health facility	5348 (86)	4563 (85.3)	1	
Private health facility	194 (3)	157 (81.1)	0.74 (0.43–1.26)	0.271
CHAM Mission	676 (11)	558 (82.5)	0.81 (0.60–1.09)	0.171
Type of delivery:				
Vaginal delivery	5032 (81)	5032 (85.3)	1	
C-Section	245 (4)	244 (76.3)	0.55 (0.39-0.79)	0.001
Parity (number of children):				
1 child	1466 (24)	1216 2.9)	1	
2-3 children	2293 (37)	1966 (85.7)	1.24 (0.96–1.60)	0.101
4–5 children	1483 (24)	1292 (87.1)	1.39 (1.08–1.79)	0.011
6+ children	975 (16)	804 (82.4)	0.96 (0.71–1.30)	0.809
Baby size:				
Not very small	6008 (97)	5107 (85.0)	1	
Very small	210 (3)	171 (81.2)	0.76 (0.49–1.18)	0.224
Density of facilities with score above 70%:				
Below mean	3820 (61)	3215 .2)	1	
Above mean	2398 (39)	2062 (86.0)	1.15 (0.95–1.40)	0.148

CHAM – Christian Health Association of Malawi, CI – confidence interval, OR – odds ratio

in **Online Supplementary Document**). The interventions with significant differences in coverage across regions are: early initiation of breastfeeding, newborns being bathed 6 hours after birth or later and newborns receiving essential newborn care visit within 2 days. In terms of the combined 'appropriate newborn care' variable, in the Northern region nearly 90% (89.5% CI = 85.5–92.6) of the newborns received at least 5 newborn care interventions followed by Central (87.7%, CI = 85.8–89.4, P<0.001) and Southern regions (81.4%, CI = 79.4–83.3, P<0.001). Coverage of all 6 of the essential newborn interventions is considerably lower across all regions. While half of all newborns (49.5%) received all 6 interventions in the Central region, coverage was recorded at 41.1% in the Northern region and 37.1% in Southern region. These unadjusted distributions take account of the complex survey design but do not consider clustering, therefore should be interpreted with caution. **Figure 2** presents coverage of the appropriate newborn care interventions measured at the district level.

The crude analysis using simple logistic regression, presented in **Table 1**, shows a positive association between appropriate newborn care and service readiness facility score of 70 and above (OR = 1.60, 95% CI = 1.25–2.03, P<0.001). Other variables found to be associated with appropriate newborn care are: residence, region, mother's education (secondary or higher), household wealth (fifth quintile), delivery by c–section and parity (having 4–5 children). For instance, newborns in the Northern and Central region of the country (as compared to newborns in the Southern part), newborns whose mothers have secondary or higher education (as compared to mothers with no education), newborns in households in the highest wealth quintile (as compared to the lowest wealth quintile) had higher likelihood of receiving appropriate newborn care in the postnatal period. On the other hand, newborns in rural areas, and newborns who were born by c–section had lower likelihood of receiving at least 5 newborn care interventions immediately after birth. There was no evidence of significant association between appropriate newborn care and mother's age at birth, type of health facility, baby size at birth or density of facilities with high score.

Multivariate analysis

The final model testing the association between receipt of appropriate newborn care and health facility service readiness score was adjusted for region, residence, household wealth, mother's education, type of delivery and baby's size at birth and residence. The results of the fully adjusted random effect logistic model are presented in **Table 2**.

Table 2. Association between appropriate PNC and district level health facility score for "normal delivery and newborn care" – random effect logistic model (N = 6218)

Variable	Categories	Adjusted OR (95%CI)	P
Health Facility Readiness Score	Bottom	1	
	Medium	1.29 (0.98–1.69)	0.067
	Top	1.52 (1.19–1.95)	0.001
Region	Southern	1	
	Central	1.53 (1.20–1.95)	0.001
	Northern	2.06 (1.50–2.83)	<0.001
C–Section	No	1	
	Yes	0.55 (0.42–0.73)	<0.001
Baby size at birth	Other	1	
	Very small	0.60 (0.43–0.84)	0.003
Household Wealth Index	Poorest	1	
	Second	1.20 (0.98–1.47)	0.070
	Middle	1.22 (0.99–1.50)	0.057
	Fourth	1.26 (1.01–1.59)	0.044
	Richest	1.37 (1.02–1.84)	0.036
Mother's education	None	1	
	Primary	1.21 (0.87–1.50)	0.091
	Secondary	1.40 (1.05–1.86)	0.023
Place of residence	Urban	1	
	Rural	0.84 (0.63–1.13)	0.254
Random effect variance (σ)		0.195	0.003
ICC (ρ)		0.011	

OR – odds ratio, CI – confidence interval, ICC – intra–cluster correlation coefficient

The analysis reveals that newborns in districts with a facility score in the top category have 52% increased odds of receiving appropriate newborn care (OR = 1.52, 95% CI 1.19–1.95, P = 0.001), compared to newborns in districts with a facility score in the bottom category. Co–variates with a statistically significant positive association with newborns receiving at least 5 newborn care interventions are: region, household wealth, mother's education. Newborns residing in the Northern region are two times more likely to receive 5 essential newborn care interventions as compared to newborns in the Southern region (OR = 2.06, 95%CI 1.50–2.83, P<0.001); the odds for newborns living in the Central region are increased by 1.5 as compared to newborns in the Southern region (OR:1.53, 95% CI 1.20–1.95, P = 0.001), having a mother with secondary or higher education increases the odds of better essential newborn care by 1.4 (OR = 1.40, 95% CI 1.05–1.86, P = 0.023) and by 1.37 if living in a household in the highest wealth quintile (OR = 1.37, 95% CI = 1.02–1.84, P = 0.036). On the other hand, newborns delivered by c–section (OR = 0.55, 95% CI 0.42–0.73, P<0.001) and very small babies (OR = 0.60, 95% CI 0.43–0.84, P = 0.003) have lower odds of receiving the type of essential newborn care analyzed in this study. This may be due to the fact that the postnatal care protocol for c–section and low birth weight babies is different [29]. Unexpectedly, even though
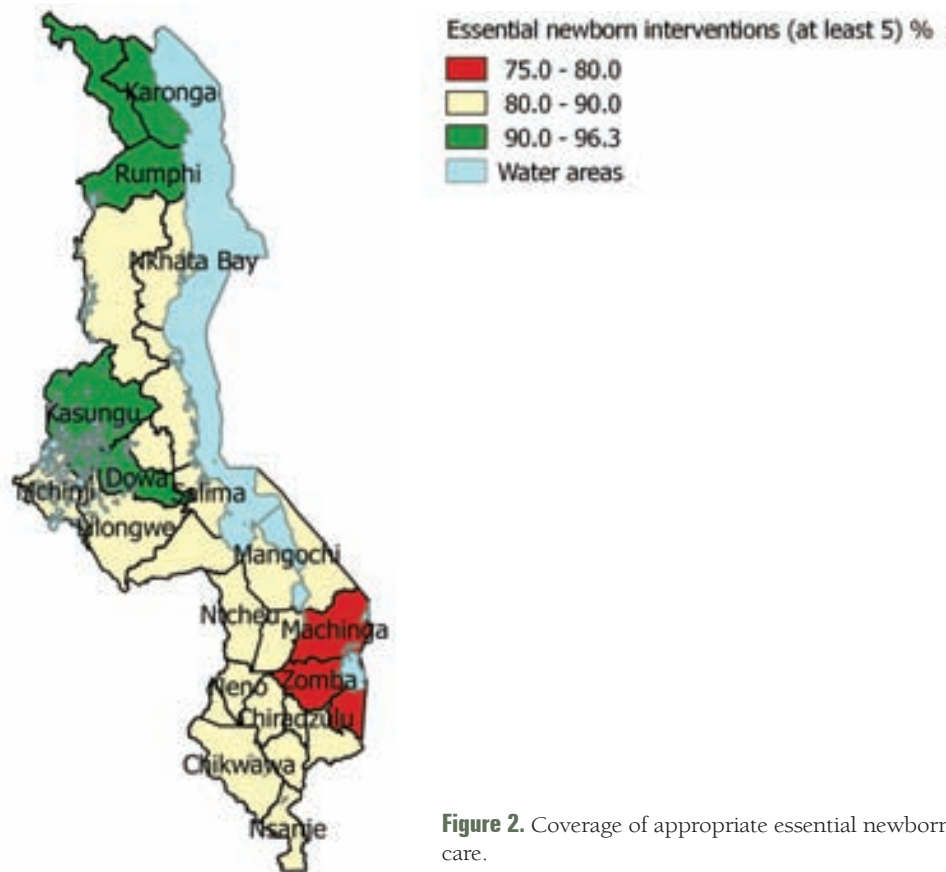
Figure 2. Coverage of appropriate essential newborn care.

residing in rural areas showed a significant effect in the crude analysis, once the model was fully adjusted this effect was lost (OR=0.84, 95% confidence interval 0.63–1.13, P=0.254).

The cluster measures calculated in the model are the random effect variance (sigma=0.195), which measures the in–between cluster variation and the intra–cluster correlation coefficient ICC (ρ=0.011). These results give an indication of clustering within districts given that the values are not zero. The random effect variance is significant (P<0.003). In other words, the result of the test of the null hypothesis of no within–district clustering provides strong evidence of within–district clustering in the model. Thus, it can be assumed that districts contributed to explain the variance in receiving appropriate newborn care.

DISCUSSION

This analysis investigated whether health facility service readiness score for normal delivery and newborn care at the district level is associated with receiving appropriate newborn care in the postnatal period in Malawi. The results indicate that newborns in districts with average facility service readiness score in the top category (score or 70% or higher) have 52% increased odds to receive appropriate newborn care than those in districts with lower facility score. The role of location is highlighted in the results as newborn in the Northern region have 2 times increased odds to receive appropriate newborn care as compared to newborns in the Southern region. As recent research has identified, addressing geographic and quality barriers is crucial to enhance service utilization and to lower maternal and perinatal mortality [30].

As reported in MSPA 2014 report, coverage of essential newborn care interventions is particularly high across health facilities in Malawi [22]. However, geographic location plays a role in the observed level of coverage disparity and health service environment. The level of health facility readiness to provide normal delivery and newborn care varies across the country (score range 56 to 80%) and only 35% of facilities across the country have a readiness score higher than 70%. A particular concern is that staff and training, which is a key domain of the health facility service readiness score is the lowest across the country. For instance, very few facilities in the Southern region have a score higher than 70% on the staff and training domain.

There are important limitations in this analysis that should be considered when interpreting the results. The measure of appropriate newborn care is based on a sub–set of recommended interventions for normal newborns for which data was available in the MES 2014 survey. Further, data on newborn care interventions is based on mother's recall of care provided to the newborn soon after birth. As with other measures based on mother's recall, this could have led to differential recall bias and may not entirely reflect the level of quality of care in facilities [31,32]. This is particularly the case for interventions that occur during the postpartum period as it is an extremely intense moment for mothers. Some mothers may not be aware of what is going on with their newborn given factors related to the dynamics of labour and delivery such as tiredness and soreness after labour, medical complications, or just the excitement of receiving their new child into the world.

Another limitation is the unavailability of GPS data at the cluster level which did not allow assessment of location within districts and distance to facilities. As the 2014 MES survey did not collect GPS data, the smallest level of aggregation possible was the district level. Districts have a number of facilities that provide different level of services. An average of the facility score at the district level may be an oversimplification of the reality. In addition, since districts are the lowest common level of geographic aggregation between the two data sets used in the analysis, further investigation of the effect of clustering at a lowest level of data collection (enumeration areas/clusters) was not possible and therefore would be a great choice for further research. To link the population and health facility data, a number of important assumptions were made. For instance, mean district health facility service readiness scores have been assigned to districts where the respondent resided at time of interview. However, this is a considerable limitation as with the available data it cannot be determined if a woman delivered in her own district or in a health facility outside of her district.

Given that this is a cross–sectional study, a cause–effect relationship cannot be established. It was also not possible to adjust for other potential confounding factors in the final model not available in the MES 2014. For instance, distance to health facility, motivation or awareness of mothers and health staff of essential newborn care procedures, availability of roads and transportation to access health facility, family support, the quality of the actual services received, women's autonomy, etc. A major confounder which could not be assessed in this study is the presence of a strong component of community–based maternal and newborn care in Malawi. For example: Ministry of Health revised the 2 week training on Community Based maternal and new born care to a 6–day training to increase coverage and improve access of these services. This process has so far covered almost 50% of the districts in the country. Supervision and mentorship tools have also been developed to support and strengthen implementation at district level [33].

Despite these limitations, the study provides evidence that the geographic proximity to facilities that provide optimal delivery and newborn care services can have an impact on the number of essential services received by the newborn. The main strengths of this analysis are the linking of health facility data with household survey data that allowed for joint analysis of health service environment and coverage indicators. Analysing these two sources of data also allowed for the inclusion of confounders at the individual, household and facility level. An important aspect of the analysis was that it looked into the quality of health facilities by analysing 3 main aspects important for normal deliveries and newborn care: staff and training, medicines and commodities as well as equipment and supplies. Previous quantitative studies have linked facility data and household data from DHS [15,34]. This methodology has a strong bearing on quality of care measurements which can use measures of essential newborn care interventions in household surveys as predictors of facility readiness.

CONCLUSION

The analysis reveals that in Malawi, newborns in districts with higher health facility service readiness score have increased odds of receiving a more complete set of essential newborn care interventions compared to those residing in districts with a lower facility score. These variations in readiness among geographical areas require a focused programming in order to address newborn care problems and achieve the targets that were set in the Every Newborn Action Plan. Therefore, it is imperative to increase the level of service readiness across all facilities, so that newborns regardless of the place and type of facility delivery receive all recommended essential interventions.

Staff availability and training emerged as an issue across all the districts in the country that can negatively affect the services received by newborns. Our study results suggest that given limited resources, prior-

ity should be given to high volume facilities in the poorly performing districts in the southern and northern regions. The essential newborn care interventions assessed in this study can for the most part be implemented with basic equipment available in most facilities and thus improvement strategies will need to address facility staff knowledge and motivation and other barriers including inadequate staffing levels. Strengthening of supervision, provision of simple job aids/checklists around essential newborn care, and ensuring adequate staffing for delivery and newborn care should be explored. In February 2017, the Malawi Ministry of Health joined eight other countries in launching a network for improving quality of care for maternal, newborn and child health and established a Quality of Care Management Directorate focussed on improving quality of care. Results of this study can help guide priority setting around what are the critical factors for the provision of quality services particularly in a context of a high neonatal mortality setting as Malawi [33]. Similarly, tracking of progress from mapping exercise and human resource development plan should be given attention as it will be critical for improvements in newborn care service delivery.

Over the last decade, the Government of Malawi has undertaken major initiatives to strengthen maternal and newborn care and improve staffing levels at health facilities. Getting performance reports and results from implementation of the current tools and instruments following the revised new born care guidelines will be a necessary as the Ministry looks forward for future domestic and international investments in health systems in Malawi. Additionally, it is critical to continue to analyse available data to generate evidence that will lead to the development of evidence based and focused programming for newborn care to the required standards in all parts of the country.

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PAPERS

Assessment of health facility capacity to provide newborn care in Bangladesh, Haiti, Malawi, Senegal, and Tanzania

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Background Despite the importance of health facility capacity to provide comprehensive care, the most widely used indicators for global monitoring of maternal and child health remain contact measures which assess women's use of services only and not the capacity of health facilities to provide those services; there is a gap in monitoring health facilities' capacity to provide newborn care services in low and middle income countries.

Methods In this study we demonstrate a measurable framework for assessing health facility capacity to provide newborn care using open access, nationally–representative Service Provision Assessment (SPA) data from the Demographic Health Surveys Program. In particular, we examine whether key newborn–related services are available at the facility (ie, service availability, measured by the availability of basic emergency obstetric care (BEmOC) signal functions, newborn signal functions, and routine perinatal services), and whether the facility has the equipment, medications, training and knowledge necessary to provide those services (ie, service readiness, measured by general facility requirements, equipment, medicines and commodities, and guidelines and staffing) in five countries with high levels of neonatal mortality and recent SPA data: Bangladesh, Haiti, Malawi, Senegal, and Tanzania.

Findings In each country, we find that key services and commodities needed for comprehensive delivery and newborn care are missing from a large percentage of facilities with delivery services. Of three domains of service availability examined, scores for routine care availability are highest, while scores for newborn signal function availability are lowest. Of four domains of service readiness examined, scores for general requirements and equipment are highest, while scores for guidelines and staffing are lowest.

Conclusions Both service availability and readiness tend to be highest in hospitals and facilities in urban areas, pointing to substantial equity gaps in the availability of essential newborn care services for rural areas and for people accessing lower–level facilities. Together, the low levels of both service availability and readiness across the five countries reinforce the vital importance of monitoring health facility capacity to provide care. In order to save newborn lives and improve equity in child survival, not only does women's use of services need to increase, but facility capacity to provide those services must also be enhanced.

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Sustainable Development Target 3.2 aims to end the preventable death of newborns and children under age 5, with specific goals to reduce newborn deaths to less than 12 deaths per 1000 live births, and under–five deaths to less than 25 deaths per 1000 live births in all countries by 2030 [1]. Recent gains in

child survival have been concentrated in the post–neonatal period, with slower gains made in survival during the first month of life [2]. As a result, the percentage of under–five deaths occurring in the first month of life has increased from 38 percent in 2000 to 45 percent in 2015 [3,4]. To continue making gains in child survival, it is essential to ensure that all newborns receive the care they need to survive.

Mothers are advised to give birth in health facilities in order to protect both their own and their infants' health [5,6]. Interventions during labor and birth, including those addressing obstetric complications, are known to have the greatest impact on neonatal survival, followed by appropriate care for small or ill newborns [7]. Specific interventions that have an impact on neonatal mortality include umbilical cord antiseptics, neonatal resuscitation, hypothermia for hypoxic ischaemic encephalopathy, topical emollient therapy, hypothermia prevention for preterm infants, Kangaroo Mother Care in preterm infants, oral and injectable antibiotics for pneumonia, and antibiotics for sepsis [7]. While evidence from a systematic review and meta–analysis suggests that delivering in a facility reduces the overall risk of neonatal mortality in low– and middle–income countries [6], not all studies have found facility delivery to be protective for newborn survival [8–10]. In fact, several recent studies using household survey data have found no evidence that the scale–up of facility deliveries or skilled birth attendance has been associated with reductions in neonatal mortality [10–12]. The provision of newborn care in the immediate and early postnatal period is particularly dependent on health facility infrastructure, capacity, and resources [13], and delivering in a facility that is ill–equipped to provide newborn care may not protect the infant. It is critical to ensure an optimal standard of care for mothers and newborns in health facilities, yet there is a gap in monitoring the quality of newborn care [14]. This study focuses on one specific aspect of quality of care: health facility capacity to provide newborn care, which is measured with service availability and service readiness to provide newborn care services. Service availability refers to the physical presence of essential newborn care services. Service readiness refers to the presence of essential infrastructure, functioning equipment, supplies, medicines that are in–stock and non–expired, trained staff, and current guidelines to provide the services. Both are prerequisite to providing good–quality services [15].

Despite agreement on the key packages and health interventions needed to protect and save newborn lives, there is little consensus on which are the key indicators needed to assess health facilities' capacity to provide newborn care [16]. The basic and comprehensive emergency obstetric care (EmOC) signal functions – shortlists of life–saving services first introduced in 1997 by the United Nations – are widely used to assess the functionality of health facility delivery care. But these functions focus primarily on provisions to treat the main causes of maternal mortality. With the exception of one recently added signal function on newborn resuscitation (introduced in 2009), the EmOC signal functions do not gauge facility readiness to provide essential newborn care [17]. Work has been under way to develop metrics for measuring facility provision of newborn care [15,16,18]. In 2008, Save the Children's Saving Newborn Lives program (SNL) convened a Newborn Indicators Technical Working Group (TWG) composed of evaluation and measurement experts, researchers, UN agencies, non–governmental organizations and donors. This group collaborated to construct a list of survey–based indicators to assess whether a facility is able to address the three leading causes of newborn death: intrapartum causes (eg, birth asphyxia), preterm birth, and infection. The evidence–based list of newborn care service indicators that they developed includes measures of service availability, equipment and supplies, documentation, staff training, supervision, and additional optional indicators [17]. Gabrysch and colleagues (2012) also proposed a set of obstetric and newborn signal functions that includes four areas: general health facility requirements, routine care for all mothers and babies, basic emergency care for mothers and babies with complications, and comprehensive emergency care functions [15]. Finally, the WHO Service Availability and Readiness Assessment (SARA) includes numerous indicators on newborn care [18]. In this study we combined indicators from these three sources to generate metrics to assess the availability and readiness of labor and delivery and immediate postnatal care provided at health facilities, in light of their impact on newborn morbidity and mortality.

The USAID–funded Service Provision Assessment (SPA) survey, implemented by the Demographic Health Surveys (DHS) Program, collects nationally–representative information about health facilities' service delivery, providing a key resource for assessing the extent to which facilities can provide comprehensive newborn care. In this study, we examined facility capacity to provide newborn care among facilities that offer delivery services in Bangladesh, Haiti, Malawi, Senegal, and Tanzania, five countries with high levels of neonatal mortality and recent SPA data. As of 2015, the neonatal mortality rates in the five countries ranged from 19 deaths per 1000 live births in Tanzania to 25 deaths per 1000 live births in Haiti, according to the UN Inter–agency Group for Child Mortality. For Senegal, Malawi, and Bangladesh, the rates were 21, 22, and 23

deaths per 1000 live births, respectively [19]. This study is the first comparative presentation of facility capacity to provide newborn care in multiple countries, using a measurable framework that could inform future studies. The manuscript originated from an earlier analysis carried out by the same authors [20] with a narrowed scope on key findings regarding newborn care service availability and readiness.

METHODS

Data

Study countries were selected according to two criteria. We focused the initial selection on the 25 USAID maternal and child health (MCH) priority countries (for a listing of the countries, see [21]). These countries account for more than 66% of global maternal and child deaths and are the focus of USAID programmatic efforts to scale up high–impact interventions and strengthen health systems [21]. We then restricted the analysis to countries with a SPA survey conducted within the last five years (ie, since 2011) with data available as of May 2016. Three of the five surveys included in the study are nationally representative sample surveys, while two (Haiti 2013 and Malawi 2013–14) are a census of all health facilities in the country (Table 1). The study was restricted to facilities that offer delivery services. Sample weights were applied throughout the study so that indicator estimates are representative of each country's actual mix of facilities, rather than the sample's mix of facilities. All five surveys produced indicators that are representative at the national level by facility type, managing authority, and geographic region.

SPA surveys provide information on the availability and readiness of health services. Specifically, the SPA surveys collect data on facility infrastructure (running water, electricity, privacy, etc.), the availability of resources (equipment, supplies, and medicines) and supportive processes and systems (client records, supervision, staff training, etc.) related to antenatal care, delivery care, and newborn care services (For more information on SPA surveys, see [22]).

SPA surveys include four standardized data collection instruments—the Facility Inventory Questionnaire, the Provider Interview Questionnaire, Observation Protocol, and Client Exit Interview—which provide general and service–specific information on the availability and quality of health services. This study relied primarily on the Facility Inventory Questionnaire, which collects information on health facilities' infrastructure, supplies, medicines, staffing, training, and procedures, as well as on the availability of specific delivery and newborn services, through interviews with the person most knowledgeable about delivery services in the facility. The study also drew upon the Provider Interview Questionnaire, which collects information on the experience, qualifications, and perceptions of the service delivery environment among health care workers who provide selected services.

Measurement of readiness

Our analysis focused on 38 tracer indicators to assess facilities' capacity to provide newborn care. In order to have this capacity, a facility must (1) offer key newborn–related services, and (2) have on–site the technology, equipment, medicine, training, and knowledge required to provide those services. Thus, we assessed two dimensions of facilities' capacity to provide newborn care: service availability and service readiness. Service availability captures the reported availability of essential newborn care services at the

Table 1. Description of SPA surveys included in the study

Country/y	Number of facilities*	Unweighted number of facilities with delivery services	Weighted number of facilities with delivery services	Sample or census
Bangladesh 2014	1548	586	280	sample
Haiti 2013	905	389	389	census
Malawi 2013–14	977	528	528	census
Senegal 2014†	363	282	279	sample
Tanzania 2014–15	1188	951	905	sample

*For all SPA surveys, the facility weights are normalized to have an equal unweighted and weighted total number of facilities.

†The Senegal 2014 SPA is part of the Senegal Continuous Survey project, which is designed to have five annual rounds of both DHS and SPA data collection, with the last round in 2017. This study uses the most recent available year of data, 2014. This survey included a subsample of health huts (case de santé). However, the methodology used to select health huts was different and their probability of selection was dependent on that of the health posts with which they were affiliated. Health huts are excluded from the current study.

facility, while service readiness captures the facility's observed capacity to provide those services [23]. We assessed three domains of service availability: the availability of basic emergency obstetric care (BEmOC) signal functions, newborn signal functions, and routine perinatal practices; and four domains of service readiness: general facility requirements, equipment, medicines and commodities, and guidelines and staffing. Table S1 in **Online Supplementary Document** presents the seven domains, lists and defines the indicators, and notes their relevance to newborn health.

The 38 newborn care indicators were drawn primarily from a list of indicators suggested by the SNL TWG, and supplemented with additional WHO SARA indicators of "basic obstetric and newborn care" [18], and with Gabrysch and colleagues' [15] proposed obstetric and newborn signal function indicators. The study did not include prevention of mother to child transmission of HIV indicators since the burden of HIV varies substantially across the study countries and HIV is not a common cause of newborn death; it becomes more relevant for the post–neonatal period [24]. Several other suggested indicators (eg, referral services for lower–level facilities) are not available in the SPA surveys, along with information on these items: resuscitation table, towel for drying the baby, or up–to–date delivery register.

In accordance with the WHO SARA approach, we computed composite indicators to assess overall newborn care service availability and readiness in the facilities. We weighted the indicators within each domain of service availability and service readiness equally to produce a domain score, and weighted each domain equally to produce a summary score for service availability and for service readiness. This simple additive scale is easily replicable.

We examined newborn care service availability and readiness nationally, as well by type of facility (hospital, health center, dispensary/clinic), managing authority (public vs private/other), urban–rural location, and region (see Section B in **Online Supplementary Document**). For managing authority, the private/other category included NGOs, Mission or religious–run health facilities, and parastatal facilities. For region, the 14 regions presented in Senegal's 2014 SPA final report were aggregated into six geographic zones to have sufficient sample size in each geographic area [25].For additional detail, refer to Tables S2a–S6g in the **Online Supplementary Document** that show the individual components that comprise the seven dimensions of newborn care service availability and readiness disaggregated by facility characteristics, separately for each country.

For the three countries with sampled health facilities, we presented confidence intervals around coverage point estimates (Stata v. 14), accounting for the SPA complex sample design. For the two countries that used censuses of all formal health facilities, confidence intervals are not needed, since the point estimates describe the full population of formal health facilities.

RESULTS

Profile of facilities with delivery services

Table 2 shows the percent distribution of facilities offering delivery services by facility characteristics and country. In all five countries, the majority of facilities with delivery services were in rural areas—ranging

Table 2. Percent distribution of facilities with delivery services by facility characteristics, Bangladesh, Haiti, Malawi, Senegal, Tanzania

	BANGLADESH		HAITI		MALAWI		SENEGAL		TANZANIA	
	%	N	%	N	%	N	%	N	%	N
Facility type:										
Hospital	26.1	73	24.1	94	18.0	95	4.0	11	4.8	44
Health Center	35.2	99	42.9	167	78.5	414	7.3	20	12.1	110
Dispensary/Clinic	38.7	109	33.0	128	3.5	19	88.7	248	83.1	751
Urban–rural:										
Urban	29.3	82	38.8	151	14.8	78	25.9	72	14.6	132
Rural	70.7	198	61.2	238	85.2	450	74.1	207	85.4	773
Managing authority:										
Public	79.8	224	50.0	195	65.7	347	89.8	251	83.6	756
Private or other	20.2	57	49.8	194	34.3	181	10.2	29	16.4	149
Total	100.0	280	100.0	389	100.0	528	100.0	279	100.0	905

from 61% in Haiti to 85% in Tanzania and Malawi. In Bangladesh and Haiti there was a fairly even distribution of hospitals, health centers, and dispensaries or clinics. In both countries, hospitals constituted roughly one–quarter of facilities with delivery services. In Senegal and Tanzania the vast majority of facilities with delivery services were either dispensaries or clinics (89% and 83%, respectively). Malawi stands out as the only country where the majority of facilities with delivery services were health centers (78%). Between 50% and 90% of the facilities were public. The managing authorities included within "private or other" varied by country, and included private, parastatal, NGO, for profit, and religious–affiliated facilities. Haiti had the largest share of private or other facilities with delivery services (50%). In Haiti these were a mix of NGO/private not for profit, private for profit, and Mission or faith–based facilities.

Overall service availability and readiness

Figure 1 shows national scores for each domain of availability and readiness, as well as national summary scores for service availability and service readiness. All scores range from 0 to 100 and indicate the average percentage of component tracer items that are available within the domain.

In all countries, of the three domains of service availability, scores for routine care availability were highest and scores for newborn signal function availability were lowest. Routine care scores ranged from about 70 in Bangladesh and Haiti to 97 in Malawi. This domain assessed the availability of three services: routine use of a partograph at the facility to monitor and manage labor, routine early initiation of breastfeeding, and routine thermal care, including drying and wrapping. While early initiation of breastfeeding and routine thermal care were nearly universal in each country, routine use of the partograph was less prevalent (see Tables S2a–S6g in the **Online Supplementary Document**).

Scores for the newborn signal function domain ranged from 26 and 27 in Tanzania and Haiti, respectively, to 55 in Malawi. Coverage of each of the three services included in the domain–corticosteroids in preterm labor, KMC for premature/very small babies, and neonatal resuscitation—was low, with the availability of corticosteroids in preterm labor scoring lowest (see Tables S2a–S6g in the **Online Supplementary Document**).

Scores for the third domain of service availability, the BEmOC signal functions, ranged from 41 in Haiti to 74 in Senegal. Of the six BEmOC functions, parenteral administration of anticonvulsants was least available in facilities, while parenteral administration of uterotonic drugs was most available (see Tables S2a–S6g in the **Online Supplementary Document**). Overall, the summary scores for newborn care service availability ranged from 49 in Bangladesh to 71 in Malawi.

Coverage patterns for the four domains of service readiness were consistent across the countries. Of the four domains, scores for guidelines and staffing were lowest, followed by scores for medicines. Guidelines and staffing scores ranged from 27 in Bangladesh to 51 in Malawi. This domain included six indicators of newborn–care related staff training, three indicators on the presence of key guidelines, and one indicator of supervision. Nearly all indicators in the domain scored poorly, with the exception of staff supervision (see Tables S2a–S6g in the **Online Supplementary Document**).

Scores in the medicines domain were also low, ranging from 28 in Bangladesh to about 60 in Malawi and Senegal. Of eight essential medicines in the domain, five were unavailable in more than half of facilities with delivery services in Bangladesh, Haiti, and Tanzania. These five medicines were chlorhexidine for cord cleaning, magnesium sulfate, hydrocortisone, injectable antibiotic, and antibiotic eye ointment for the newborn (see Tables S2a–S6g in the **Online Supplementary Document**).

Within each country, scores for the general requirements and equipment domains were higher, and were similar to each other. General requirements scores ranged from 50 in Tanzania to 66 in Malawi. This domain included five indicators: the availability of emergency transport, 24/7 skilled birth attendance, improved sanitation, an improved water source, and electricity. Of these, 24/7 skilled birth attendance was least prevalent, followed by emergency transport and improved sanitation (see Tables S2a–S6g in the **Online Supplementary Document**).

Equipment scores ranged from 53 in Tanzania to 69 in Malawi. The domain included 13 indicators, including sterilization equipment, delivery bed, examination light, delivery pack, suction apparatus, manual vacuum extractor, vacuum aspirator or D&C kit, partograph, disposable latex gloves, newborn back and mask, infant scale, blood pressure apparatus, and handwashing soap and running water or hand disinfectant. Of these, facility coverage of manual vacuum extractors and vacuum aspirator or D&C kits tended to be lowest, followed by newborn bag and masks and sterilization equipment (see Tables S2a–

Figure 1. National service availability and service readiness summary scores, Bangladesh, Haiti, Tanzania, Malawi, Senegal. Confidence intervals are not shown for Haiti or Malawi, since those surveys were a census of all formal health facilities.

S6g in the **Online Supplementary Document).** Overall, the summary scores for newborn care service readiness ranged from 42 in Bangladesh to 62 in Malawi.

Figure 2 presents differentials in the composite service availability and service readiness scores side by side. The patterns in service availability and service readiness are strikingly similar across countries. Scores for both service availability and service readiness tended to be highest in hospitals and in urban areas. There

Service availability summary score

Service readiness summary score
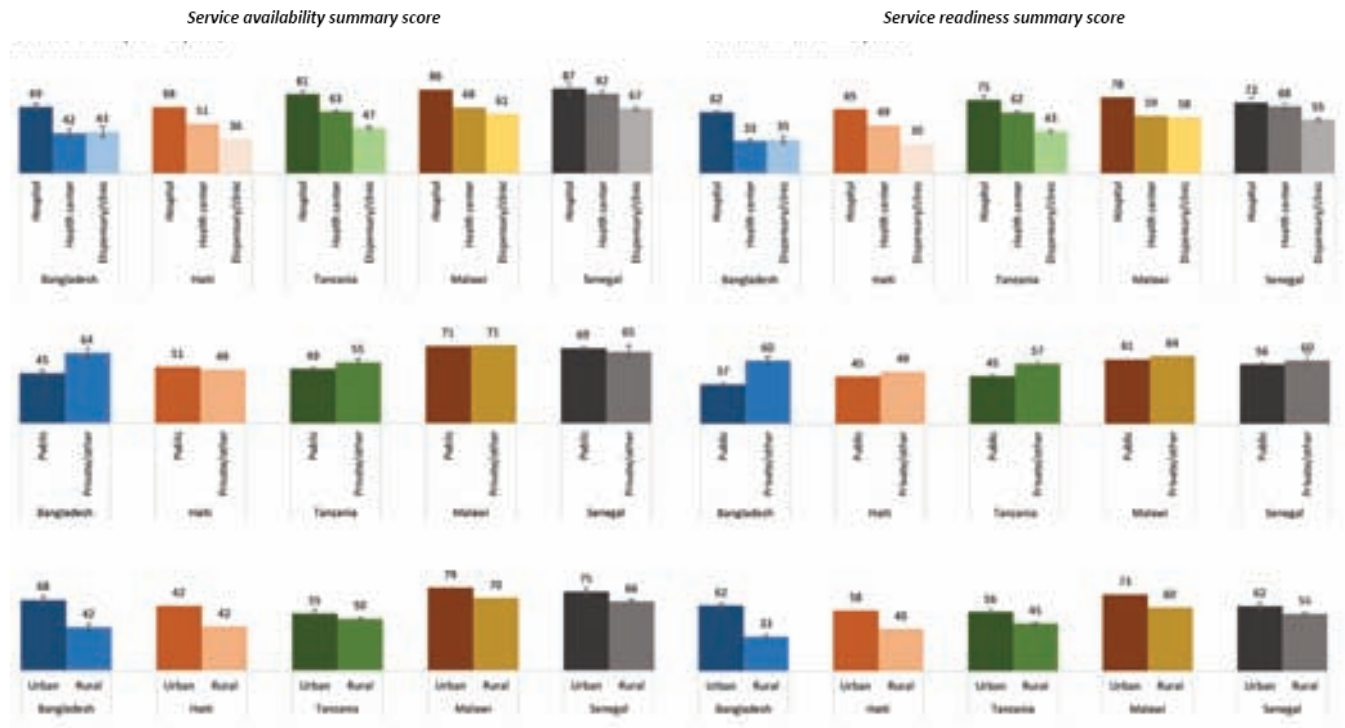
Figure 2. Service availability (panels on left) and service readiness (panels on right) summary scores by facility characteristics, Bangladesh, Haiti, Tanzania, Malawi, Senegal. Confidence intervals are not shown for Haiti or Malawi, since those surveys were a census of all formal health facilities.

was less difference in scores between public and private facilities, except for Bangladesh and Tanzania, where private facilities scored notably higher for both service availability and service readiness. To see the individual components that comprise the seven dimensions of newborn care service availability and readiness disaggregated by facility characteristics, see Tables S2a–S6g in the **Online Supplementary Document**.

DISCUSSION

Where you are born strongly affects your chance of survival [26]. Previous studies have found that access to delivery care alone is not enough to reduce early neonatal mortality rates [8]. It is essential that the facility where the birth occurs be equipped to provide key life–saving services for the newborn. Our study is the first study to examine the capacity of facilities to provide newborn care in five countries with high neonatal mortality. In all five countries, key services, commodities, and medicines needed for comprehensive delivery and newborn care were missing from a large proportion of the facilities that offer delivery services. This is important not only because it indicates a likelihood of poor quality of care, or possibly no care, but also because widespread perceptions of services of poor quality can deter women from seeking any care at a facility [27].

Of the five countries assessed, Malawi had the highest scores for both service availability and service readiness. Service availability scores in Malawi varied by domain, with the lowest scores being for BEmOC signal functions and newborn signal functions. Service readiness domain scores were generally consistent, at around 60. However, a need for improvement remains for all domains except routine care. Hospitals scored the highest for service availability and service readiness, while health centers scored much lower. Because health centers constitute nearly 80% of the facilities that provide delivery services, and they have the potential to serve more people than hospitals, further investment in the availability and readiness of their newborn care services is greatly needed. Urban facilities generally scored higher than rural facilities, and there was only a slight difference between public and private facility scores. Most facilities are located in rural areas (85%), and investments to increase the scores of those facilities in Malawi could have a significant impact on the population. Our findings are consistent with a study by Zimba and colleagues (2012) that found most facilities had staffing and supply shortages and lacked three or more signal functions [28].

Senegal's newborn care quality scores were nearly as high as those in Malawi, at 68 points for service availability and 57 points for service readiness. Senegal's highest score was for routine care (89); its lowest scores were for guidelines and staffing (38) and the availability of newborn signal functions (43). Compared with the other countries, disparities are markedly less drastic in Senegal. There was little difference between public and private facilities in service availability and readiness, and on average the differences between urban and rural facilities are smaller than for other countries except Malawi. Still, health posts—which constitute nearly 90% of all facilities that offer delivery services and 100% of the "dispensaries and clinics" category–scored substantially lower than hospitals. Investments to increase the scores of health posts could have a significant impact on population health.

Bangladesh showed impressive reductions in neonatal mortality between 1990 and 2015, with the NMR declining steadily and incrementally from 63 deaths per 1000 live births in 1990 to 23 deaths per 1000 live births in 2015 [19]. Despite this improvement, we found that the country had relatively low scores for newborn care service capacity, with scores below 50 for both service availability and service readiness. Its highest score was for routine care (70) and its lowest was for the availability of medicines (28). Of the five countries, Bangladesh also showed the widest gaps in coverage across subgroups: hospitals generally had much higher scores than health centers or dispensaries/clinics; private facilities had higher scores than public facilities, and urban facilities had higher scores than rural facilities, suggesting geographic and economic inequities in access to high–quality newborn care. These findings are consistent with other studies that reported inadequate quality of obstetric care in the country and marked urban–rural gaps in quality [29]. Bangladesh has been a global leader in prioritizing newborn survival and care [30], and its policy efforts have been highly successful, as evidenced by the reductions in NMR. The relatively low quality scores could be explained by the country's newborn care policy emphasis on community health workers and home and community–based interventions [30]. That emphasis makes sense given that 62% of women in Bangladesh deliver at home, according to the 2014 Bangladesh DHS [31]. However, given that the remaining 38% of women deliver in health facilities, concentrated efforts to improve the quality of newborn care in health facilities are urgently needed, and could lead to further reductions in neonatal mortality.

Tanzania also scored around 50 for overall service availability and service readiness, with its highest score attained for routine care (80) and its lowest score for newborn signal functions (26). Hospitals, which constitute just 5% of the country's health facilities with delivery services, had higher scores than health centers or dispensaries/clinics; private facilities had higher scores than public facilities; and urban facilities had higher scores than rural facilities, suggesting both geographic and economic inequities. While Tanzania made impressive gains in child survival between 2000 and 2015, improvements in neonatal survival were far slower [32]. Afnan–Holme and colleagues (2015) reported important differences in funding and implementation strategies among child, maternal, and newborn health policies in Tanzania that could have contributed to these different trajectories [32]. Child survival began receiving consistent policy attention in the mid–1980s, while attention to maternal health came later, in the mid–1990s, and attention to newborn care even later, in 2005. While Tanzania's child survival policy strategy has focused primarily on implementing high–impact interventions at the first level of the health system, maternal health interventions have often been targeted at higher levels of the health system [32]. Newborn care policies are just now rapidly scaling up in Tanzania [32]. These policies should target newborn care readiness at all facility levels, with an emphasis on first level facilities where readiness is currently lowest, and where more than 30% of women deliver [33].

Haiti scored around 50 for both service availability and service readiness, with a highest score of 68 for routine care and a lowest score of 27 for newborn signal functions. Overall in Haiti, public and private facilities scored similarly, but hospitals scored higher than health centers and dispensaries/clinics, and urban facilities scored higher than rural facilities, signaling geographic inequities and probable barriers to access. These findings are consistent with those of Wang and colleagues (2014), who also found that lower–level facilities in Haiti—and specifically health centers without beds and dispensaries—are poorly prepared to provide delivery services. In Haiti, health centers without beds and dispensaries lack a government mandate to provide delivery services [34], yet these facilities constitute half of all facilities that report offering delivery care [35]. Facilities that lack an official mandate may not receive necessary support from the government. Since lower–level facilities are often the only option in rural areas, the government should formally include them as providers of delivery care and equip them with the medicines, commodities, personnel, and training necessary to provide high–quality delivery and newborn care [35].

The study has several limitations. Our choice of countries was limited by the availability of SPA surveys. With data from SPA surveys, we cannot assess all aspects of the quality of newborn care. In this study we

focused on two measurable dimensions of quality: service availability and service readiness. These two dimensions are necessary—but not sufficient—components of providing high–quality newborn care. While the indicators used to measure service availability and readiness were suggested by global experts in the field, there is a lack of evidence on a few indicators (eg, recent staff training in neonatal resuscitation, use of corticosteroids in preterm labor) about their association with newborn health outcomes. Furthermore, the service availability and readiness scores we created include 38 tracer indicators and condense a great deal of information that needs to be "unpacked" for clear interpretation and program purposes. However, we believe the scores provided a valid way to summarize a large amount of related information. The strength of our study is our multifaceted analysis, through which we sought to expose the current status of two components of newborn care quality from different angles.

We conclude that facility capacity to provide newborn care is lacking in five countries with a high burden of neonatal mortality. Of the seven domains of service availability and service readiness studied, routine care consistently scored highest, while newborn signal functions and guidelines and staffing tended to score lowest. The results point to persistent inequality in access to high–quality newborn care between urban and rural areas and between hospitals and the more commonly used health centers and dispensaries/clinics. Health system initiatives to improve facility capacity are needed in each of the five countries. All facilities that offer delivery services must have trained staff available around–the–clock and be equipped with the essential supplies, medicines, and commodities needed to care for the mother–newborn dyad during labor, delivery, and the immediate postnatal period.

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