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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, policymakers 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*

Miners from around Bolivia went on strike in the summer, congregating in La Paz. They were fighting for better workers' rights and working conditions. Things are improving in the world of mining, with improved safety standards and public awareness of the dangers involved. However, mining remains one of the most dangerous occupations in the world, with people from developing countries being particularly exposed.

Submitted by: Christopher Graham, EUGHS member. The photo won the 2nd prize in the Journal of Global Health's annual photo competition in 2014.

Assembling GHERG:
Could "academic crowd–sourcing" address gaps in global health estimates?

Igor Rudan[1], Harry Campbell[1], Ana Marušić[1,2,3], Devi Sridhar[1], Harish Nair[1], Davies Adeloye[1], Evropi Theodoratou[1], Kit Yee Chan[1]

[1] Centre for Global Health Research, The Usher Institute for Population Health Sciences and Informatics, University of Edinburgh, Scotland, UK
[2] Croatian Centre for Global Health, University of Split School of Medicine, Split, Croatia
[3] Department of Research in Biomedicine and Health, University of Split School of Medicine, Split, Croatia

In recent months, the World Health Organization (WHO), independent academic researchers, the Lancet and PLoS Medicine journals worked together to improve reporting of population health estimates. The new guidelines for accurate and transparent health estimates reporting (likely to be named GATHER), which are eagerly awaited, represent a helpful move that should benefit the field of global health metrics. Building on this progress and drawing from a tradition of Child Health Epidemiology Reference Group (CHERG)'s successful work model, we would like to propose a new initiative – "Global Health Epidemiology Reference Group" (GHERG). We see GHERG as an informal and entirely voluntary international collaboration of academic groups who are willing to contribute to improving disease burden estimates and respect the principles of the new guidelines – a form of "academic crowd–sourcing". The main focus of GHERG will be to identify the "gap areas" where not much information is available and/or where there is a lot of uncertainty present about the accuracy of the existing estimates. This approach should serve to complement the existing WHO and IHME estimates and to represent added value to both efforts.

Rapid development of information technologies in the past two decades has brought about major improvements in the generation, sharing and analysis of information on the health status of the entire human population. This has facilitated the development of the field of "Global Health Metrics", which has its champions in World Health Organization's Mortality and Burden of Disease Unit and University of Washington's Institute for Health Metrics and Evaluation (IHME). A number of other groups, initiatives and institutions also contribute substantially to this field and regularly publish population health estimates. These include national epidemiological services, population–specific (eg, occupational, ethnic, age–and gender–defined) and disease–specific registries, academic research groups interested in specific health problems, pro-fessional societies that specialize in a particular disease(s), and initiatives by international organizations.

Examples of organizations specializing in population health surveillance that require health metrics as a starting point include the United States Centers for Disease Control and Prevention (USCDCP), European Centre for Disease Prevention and Control (ECDPC), Chinese Center for Disease Control and Prevention (CCDCP), International Agency for Research on Cancer (IARC) and the United Nation's Children Fund (UNICEF). All of these organizations regularly publish summaries of large amounts of information on population health that is collected through their services. Moreover, the Demographic and Health Surveys (DHS) Program, supported by USAID, continues to collect, analyze and disseminate representative data on population,

health, HIV, and nutrition through more than 300 nationally–representative household surveys in over 90 countries. Similarly, UNICEF assists countries in collecting and analyzing data on health of women and children through its household survey program called Multiple Indicator Cluster Surveys (MICS).

Further to these efforts, professional societies such as the International Diabetes Federation (IDF) and Alzheimer Disease International (ADI) work together with the World Health Organization to develop and regularly update the global, regional, and sometimes national estimates of type 2 diabetes and dementia, respectively. There are many other examples of successful collaborations between international agencies and academic research groups in order to develop accurate and transparent population health estimates. Some of the most notable examples are the United Nation's Inter–Agency Group for Child Mortality Estimation (IGME), and the Child Health Epidemiology Reference Group (CHERG), in which our group in Edinburgh has also been involved for the past decade. IGME regularly revises the overall child mortality estimates at the national level, while CHERG made major contributions to the understanding of the leading causes of child deaths globally, regionally and nationally. CHERG's work provided much needed evidence to inform and help direct policies towards achieving UN's Millennium Development Goal 4. CHERG developed into a collaboration between the WHO, UNICEF and a group of independent technical experts from leading academic institutions who worked together to assemble available information on the causes of child deaths in parts of the world where there was no adequate vital registration coverage. An important aspect of CHERG work was to critically review this information and to include only data which met stated quality criteria regarding validity and representativeness.

In addition to understanding the burden of disease in human populations, determinants of the burden – ie, the underlying risk factor causes that make people ill – are also of interest to the field of global health metrics. Several countries or regions have set up large–scale biobanks in recent years to study determinants of population health on a very large scale, using a "big data" approach. Some of the most impressive examples are UK Biobank, the Kadoorie biobank in China, and the EPIC prospective study in Europe. Each one of these biobanks includes about 500 000 persons which should give them sufficient study power to tease out the effects of many different potential environmental, genetic and lifestyle contributors to human diseases. Likewise, there are academic groups that regularly review and assess the scientific literature to identify risk factors through large meta–analyses, such as the INTERHEART Study which evaluates risk factors for myocardial

infarction (MI), or Environment and Global Health Research Group at the Imperial College London, which collaborates with the WHO to provide national–level updates on risk factors such as the prevalence of obesity, hypercholesterolemia, hypertension and hyperglycaemia.

The "big data" approach to global health metrics, currently championed by IHME and increasingly adopted by other groups, should work well over time. The application of sophisticated analytical methods to these massive data sets should be expected to yield population health estimates that would continuously improve over time. However, there are also problems with reliance on "big data" and the field of global health metrics is particularly prone to some of the most frequently highlighted concerns [1]. The much larger amount of data under study will not necessarily make the estimates of disease burden more accurate if most of the data are systematically biased. Moreover, there is a false assumption that very large amount of data automatically implies that the collection will cover all parts of the world adequately and represent underlying populations well. Unfortunately, the global health data available in the public domain today suffers from both these problems. Despite the increasing availability of massive data sets of population–based data the field of global health metrics still faces a number of important challenges.

First, a lot of population health data that is readily available in the public domain, or to organizations such as the WHO or IHME, are national–level estimates based on reporting to national epidemiological services. There is a possibility that these estimates suffer from systematic under–reporting, resulting in estimates that are much lower than the actual situation, even although they are based on very large amounts of data. Second, although the current global health estimates by both WHO and IHME for 2013 make a laudable attempt to model the estimates at the national level for each country in the world, this gives a false impression that there is relevant information available from all these countries. In reality, there are some parts of the world in which there is an abundance of information and the estimates are very precise. However, there are also other regions, and also certain diseases and risk factors, for which the amount of information is remarkably scarce. For some of these countries (or sub–national areas) and conditions the situation has not improved over the past 20–30 years, leading to very large degrees of uncertainty in disease burden estimates. The investment in and development of ever more sophisticated methods of computation and/or epidemiological modeling is less important to achieving valid disease burden estimates – which reflect the true burden in the world population – than investment in generating a sufficient amount of reliable information in those countries and conditions.

These inherent uncertainties are further compounded by the lack of complete transparency from the IHME over their input data that could allow other investigators to replicate their computations and assess the true amount of uncertainty in many of their estimates. In fairness to IHME, though, very few researchers outside the field of global health metrics can truly comprehend the scale of their effort and the size of their data sets, so it is perhaps not surprising that they may feel that they need to continue to refine their data sets and methods through further iterations before they are ready to fully expose them to the rest of the global health research community. [2] However, as long as they do not open their input data and all their methods to a full independent replication by other legitimate academic groups, who do understand these issues – and there are several groups that could do this – it will continue to be difficult for the global health community to fully accept IHME's estimates. Consistent replication of any scientifically produced result by independent research groups has been a norm in other fields of science, making the key difference between an initial report and a broadly accepted new knowledge. In the end, IHME should benefit more than any other parties from opening their work to other groups – from getting an independent review and feedback on their work, to gaining scientific legitimacy and obtaining suggestions on where to focus further efforts to continue improving their estimates.

In recent months, the WHO and IHME have started to work together with a group of independent academic researchers from this field and senior staff from the *Lancet* and *PLoS Medicine* journals to improve the reporting of population health estimates and, through this, improve the accuracy and transparency of estimates. The new guidelines – likely to be named GATHER (which would stand as an acronym for the "Guidelines for Accurate and Transparent Health Estimates Reporting") – should improve practices of both those who generate and report primary information on health estimates and those who assemble the primary information and model it to develop global, regional and national health estimates for diseases and risk factors. Once adopted fully, the new reporting guidelines will represent a very helpful step forward that should benefit the field. Successful collaboration of the WHO and IHME teams and international academic experts (including from our Centre for Global Health Research in Edinburgh) on finalizing these guidelines would be a very welcome development, especially if adherence to such guidelines becomes a requirement for publication in all the leading medical journals [3].

We may conclude that, at this point, many positive developments are occurring in the field of global health metrics. The introduction of "big data" approaches, the development of more sophisticated and improved analytic methods, and improved use of new information technologies for data storage and visualization are all contributing to progress. The introduction of new guidelines should add to this progress and generate more papers with primary health data that would be of sufficient reporting quality to be useful for inclusion in different epidemiological models. They will also help to clarify which input data are being used in the models and how the models work.

However, as noted above, there is also a need to increasingly focus on how to generate a lot more information on disease burden and risk factors from "gap" areas of the world. This is particularly true for diseases and risks on which there is hardly any data or epidemiological research in recent decades, and where none of these elements of progress will be able to lead to trustworthy estimates. Possible approaches to address these gaps will need to include research capacity building in gap countries and regions in conducting and reporting epidemiological research. A network of international medical journals interested in global health – such as our *Journal of Global Health* – could play a substantial role in this capacity building. There is a need to educate both the researchers and the journal editors in less developed regions of the good practices and adherence to new guidelines in reporting their health estimates. It is possible that new technologies – such as mHealth and eHealth, ie, the use of mobile phones and internet to gather information – may also enable forms of "crowd–sourcing" approaches to generate population health data in the areas of the world where no other approaches can guarantee success and to understand burden of health problems in real time.

In recent years, our Edinburgh–based group has "specialized" in finding useful health information and developing population health estimates for epidemiologically under–researched problems and areas [4]. This led to the award of the status of the World Health Organization's Collaborating Centre for Population Research and Training. Our "gap–filling" efforts include trying to learn more about the emerging and alternative sources of medical literature and health information, such as recently digitalized Chinese medical databases CNKI, WanFang, VIP and others. This led to much improved estimates for several major health issues in transitioning China, such as a dramatic reduction of child mortality and its likely causes [5,6], a much finer resolution of the causes of mortality from childhood accidents [7], or the first comprehensive estimates of the burden of dementia [8] and schizophrenia [9] among the adult and elderly Chinese population. For the African continent, we have provided estimates of dementia, COPD, epilepsy, colorectal cancer and rheumatoid arthritis. Likewise, for South Asia, we have published estimates for type 2 diabe-

tes [10–14]. In this current journal issue, we are also publishing a study that estimated of the burden of rheumatoid arthritis in LMICs that was largely based on information from non–English databases and the so–called 'grey literature' [15]. We used similar approaches to develop global, regional and, national (wherever allowed by data) estimates for rather neglected and under–researched problems in global health such as childhood pneumonia [16,17], peripheral arterial disease [18] and sequelae from childhood meningitis [19].

Perhaps even more relevant to this "gap–filling" agenda, our group in Edinburgh also pioneered the approach of "academic crowd–sourcing" to address some health issues of specific interest, for which remarkably few data are available in the public domain. As an example, in our attempts to estimate the global, regional and national burden of RSV and influenza infections in children – both of which are important because of a possible opportunities for immunization – we gathered a group of well–minded independent experts who were in possession of either published or unpublished useful information on these under–researched topic, and who agreed to share these data for the purposes of developing global, regional and national estimates [20–22]. Through this approach, we have found out that there is much more useful information available than could be concluded based on reviews of published sources. However, many of the most useful data sets were from studies established for other purposes such as data from control arms of randomized controlled trials which have a disease of interest as an outcome, or data from surveillance systems such as that set up to monitor the evolution of influenza and act as an alert mechanism for viruses with pandemic potential. Mobilizing these valuable sources of data have greatly improved that information available to burden of disease models compared to what was available solely through publically available sources [20–22].

This is precisely where we would like to position a new initiative – the "*Global Health Epidemiology Reference Group*" (GHERG). We would like to propose an informal and entirely voluntary international collaboration of academic groups willing to contribute to improving disease burden estimates to complement IHME activities and who agree to respect the principles of the new guidelines – a form of "academic crowd–sourcing". Most importantly, all the input data, methods and work should be fully transparent and accessible to all other qualified researchers to verify and replicate them. Ideally, all GHERG papers should have more than one research group involved, and all of the collaborating groups would need to have full access to data. GHERG should, therefore, become an extension of Child Health Epidemiology Reference Group (CHERG), aiming to address global health issues in age groups beyond 0–4 years.

The overall goal of GHERG will be to develop and deploy new and improved evidence on the causes and determinants of morbidity and mortality among populations in all world regions, on the importance of a broad range of risk factors, and on the effectiveness of public health interventions, to inform and influence global priorities and programs. The main focus will continue to be on identifying the "gap areas" where not much information is available and where there is a lot of uncertainty present about the accuracy of the existing estimates. This approach should serve to complement the existing WHO and IHME estimates and to represent added value to both efforts.

The main purposes of the GHERG will be to publish papers, reports and reviews on global health epidemiology, with a special focus on identifying information of sufficient quality in low and middle–income countries and filling the gaps in information for regions where the data are very scarce and of insufficient quality. Also, we would like to advise WHO and other international organizations, institutions and initiatives on the most appropriate methods and assumptions for their global, regional and country level epidemiological estimates. We will aim to advise researchers and public health officials on the different issues involved in the estimation of cause–specific morbidity and mortality.

The core membership of GHERG will initially be offered to the editors and regional editors of the *Journal of Global Health*, who are all independent researchers working for the leading academic institutions. However, GHERG will be open to literally everyone to contribute their data, methods and estimates. It will aim to serve global health community by providing unrestricted open access to its data sets, methods and publications, and continuously revising and updating global health estimates for a targeted set of conditions.

Accurate global health estimates are extremely important because they expose the key issues, inform health policies, direct funding disbursements and eventually solve problems and save lives. In that sense, they could be viewed as a "matter of life and death". Because of this, when it comes to global health estimates, we see value in both collaboration and competition. Two, three or even more estimates of the same problem, generated by independent research groups, are certainly more informative and helpful than only one – especially if all of them are fully transparent and their methods can be compared [2]. If the principles of the new guidelines are respected by all research groups in the field, then all different estimates would eventually be expected to converge to the same, reliable set of estimates that we are hoping to deliver to the global health community for their unrestricted use.

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EDITORIAL

Correspondence to:
Igor.Rudan@ed.ac.uk

▶ Africa

▶▶ Almost 4000 Liberians died in the recent Ebola outbreak, but thanks to behavioural changes and massive international aid efforts, there are only six confirmed cases of Ebola left in the country. As a result, commercial activity is returning to normal, and schools and hospitals are beginning to re–open. Stephen Kennedy, a Liberian doctor, symbolises the new spirit of hope and resilience in Liberia. He is spear–heading a new vaccine trial that could prevent future outbreaks. "I feel so excited. This is something I have dreamed of – to help my country make a major contribution to international public health," he says. (*BBC*, 2 Feb 2015)

▶▶ Sierra Leone's national auditor, Lara Taylor–Pearce, states that government ministers lost US$ 3 million of internal emergency funds to fight Ebola, with another US$ 2.5 million incompletely accounted for. This led to "a reduction in the quality of service delivery in the health sector." These funds were from taxes and donations from individuals – mainly in Sierra Leone – and excludes UN and aid agency funding. According to the BMJ, one–third of the US$ 2.9 billion pledged by international donors had not reached Sierra Leone, Guinea and Liberia by the end of 2014; and the UN is seeking an additional US$ 1 billion of aid to contain Ebola. (*New York Times*, 14 Feb 2015)

▶▶ The South African research consortium Follow–on Africa Consortium for Tenofovir Studies (FACTS) found that a microbicide gel believed to reduce the risk of a woman being infected with HIV during sex is ineffective. This in contrast to a 2010 study which suggested the gel reduced infection rates by 39%. The e gel contains the antiretroviral compound tenofovir, and is applied to the rectum or vagina to protect against HIV and other sexually transmitted infections. There are currently no commercially–available microbicide gels, although WHO figures show that 23 are being clinically tested. The gel's effectiveness could be undermined by application problems – emphasizing the need for women–centred HIV–prevention methods. (*Mail and Guardian*, 23 Feb 2015)

▶▶ Hifikepunye Pohamba, Namibia's outgoing President, won the Mo Ibrahim Prize for "good governance" in Africa. The US$ 5 million is given to a democratically–elected former head of state who left office in the previous 3 years, and has demonstrated "exceptional leadership" whilst abiding by constitutional term limits. Mr. Pohamba has been lauded for reconciling with opponents, pushing for gender equality in politics, and increased expenditure on housing and education. Salim Ahmed Salim, chair of the prize committee, singled out Mr Pohamba's "sound and wise leadership" and "humility" during his presidency. The prize had only been awarded on three occasions, due to many African leaders seeking to stay in power as long as possible. (*yahoo news*, 3 March 2015)

▶▶ The African Union (AU) criticised the international media for overlooking Africa's efforts to tackle Ebola, instead focusing on international agencies and those with the greatest media clout. Dr Olawale Maiyegun, director of Social Affairs at the AU, claimed that Africa had taken the lead in the most critical human resources for health (it deployed 835 health workers to the affected countries), whilst most of the international community focused on finance and infrastructure efforts. However, the AU has faced criticism for holding an emergency summit 10 months after the outbreak of Ebola. Dr Maigegun responded by saying that the AU's response was guided by the affected countries. "We put volunteers at the disposal of the affected countries. They told us what to do and we have performed creditably," he said. (*The Guardian*, 7 April 2015)

▶ Asia

▶▶ In Nov 2014, Indonesia's new government (led by President Joko Widodo) began issuing cards to give poor Indonesians access to expanded publicly–funded health care and education programmes, and access to an income top–up scheme worth US$ 15.75 a month. The top–up scheme will eventually reach one–third of Indonesia's population – or 86.4 million people – making it the largest such programme in the world, and could lift millions out of poverty. The programme is financed by ending petrol subsidies, which disproportionately benefitted wealthier Indonesians. Although there are logistical challenges in providing services across such a vast dispersed country, and in using mobile technology to collect top–up payments, in the long–term the scheme could make Indonesians healthier and better–educated – and ultimately wealthier. (*The Economist*, 8 Jan 2015)

▶▶ The Population Council Pakistan carried out two studies on the country's induced abortions and unintended pregnancies, and low rates of contraceptive use in collaboration with the Guttmacher Institute USA. They uncovered rising rates of induced abortions and unintended pregnan-

cies in women aged 15–49 years, jumping from 27 per 1000 women in 2002 to 50 per 1000 in 2012. In 2012 alone, 4.2 million out of 9 million pregnancies were unintended, with 54% ending in abortion and 623 000 women being treated for post–abortion complications. This is against a background of low rates of contraceptive usage, and high discontinuation rates. The studies' partners say that the unmet need for birth control was a major cause of increasing abortion rates – risking women's lives – and there is a real need to reduce the gap between the supply and demand for contraceptive services. (*The Express Tribune*, 29 Jan 2015)

▶▶ According to the World Economic Forum (WEF), Indonesia is now South East Asia's largest economy, but non–communicable diseases (NCDs) threaten it with a US$ 1 trillion burden – more than five times its 2012 GDP. In 2014, deaths from NCDs accounted for 71% of all deaths – up from 51% in 2004. The WEF believes that the ageing Indonesian population and rapid urbanisation – with its associated prevalence of risk factors like tobacco, harmful alcohol use, poor diet and sedentary lifestyles – underpins this increase. Indonesia's output loss from NCDs is higher than China and India. However, investing in health interventions to reduce NCDs have high returns, both socially and economically. (*CNBC*, 20 Apr 2015)

▶▶ Cambodia is one of the world's fastest–growing economies, with average growth at 7% per annual, income levels of nearly US$ 1000 per capita, and poverty has fallen from 50% of the population to 20%. Economic growth has been accompanied by major improvements in the country's health – during 2000 – 2012, life expectancy increased from 61.9 years to 71.4 years, the infant mortality rate fell from

95 to 28, the under–5 mortality rate declined from 124 to 35 during 2000 – 2012, maternal mortality rates fell from 437 to 170, and attended births rose from 50% to 89%. Many communicable diseases (eg, HIV, malaria) are largely under control. However, major challenges remain, with disparities between urban and rural areas, and health outcomes do not yet match other countries in the region. Poor water and sanitation, high neonatal mortality and malnutrition persist. The government is providing health equity funds to enable free access to health services for those in need, and 2 million people are now covered. The country's health planners aims to extend health coverage, improved training and licensing of health workers, and stronger monitoring and evaluation. (*SciDev.net*, 23 Apr 2015)

▶▶ The death toll from the earthquake which struck Nepal has passed 7 500, and will become higher as rescue teams reach isolated villages. Aid agencies report that Nepalese local governments are overwhelmed, as it has been 80 years since the country's last comparable disaster. Médecins Sans Frontières (MSF) report that more aid is reaching areas outside the capital, Kathmandu, as the challenges from getting aid from the bottlenecks at Kathmandu ease. According to the UN, 8 million out of Nepal's 28 million people were affected by the earthquake, and at least 2 million need tents, water, food and shelter. "Our priority is to reach people in places where no one else is going and who have not received assistance. So it has been a huge challenge logistically to get the necessary supplies in through the congested airport, and secure the air transport we need to be able to provide medical assistance and deliver shelter and relief materials to the people in most urgent need," says MSF's Dr Prince Mathew. (*Irish Times*, 6 May 2015)

▶ Australia and Western Pacific

▶▶ Refugees from Africa, the Middle East and South Asia who are held on the Pacific island of Nauru after being declined by Australia could be offered payment by the Australian government to settle in Cambodia. This is part of a wider Australian policy of deterring refugees from reaching Australia by boat, and is condemned by human right activities as inhumane and potentially dangerous. As yet, no refugee has accepted the offer, which includes cash, help in finding work, access to education, language training, accommodation and health insurance. (*ABC News*, 17 Apr 2015)

▶▶ Australia removed a religious exemption that allowed parents unwilling to immunise their children from claiming certain benefits, and unveiled a US$ 20 million pack-

age to increase child vaccination rates. More than 39 000 children under 7 years were not immunised due to the parents' objections – an increase of 24 000 over the past 10 years. Australia has a vaccination rate of over 90% for children aged 1–5 years, and in 2014 at least 166 000 children were recorded as overdue for immunisation for more than two months. Other measures to boost immunisation include the establishment of a national school vaccination register and financial incentives for doctors to follow–up on children late for vaccinations. An anti–vaccination movement has coincided with increasing cases of measles in parts of Europe and the USA. Many people avoid immunisation for their children over concerns over the triple vaccines for measles, mumps and rubella alleged link to

autism – a theory which has been repeatedly disproven. (*AFP*, 19 Apr 2015)

▶▶ The New Zealand government is facing accusations of reneging on an election promise to provide free GP visits for primary school children. Documents obtained by the country's Green Party show that the government is funding only 90% of doctors' visits for children suffering from an injury. Government ministers replied by stating that they expect uptake to eventually become universal, and that it has provided an additional US$ 21 million of funding to doctors to encourage them to provide free visits for children aged under 13 years. Moreover, some doctors in wealthier areas charge patients an additional fee on top of their government payment. (*stuff.co.nz*, 21 Apr 2015)

▶▶ Healthy volunteers are taking part in a trial at the University of Queensland, where they are infected with low doses of malaria to test the efficacy of new drug treatments. This accelerates the development of new drugs, saving money in R&D costs and provides hope for the development of more effective vaccines. Under this testing model, volunteers are injected with a sample of malaria that is much smaller than that transmitted by a mosquito bite. They are closely monitored using tests to measure the DNA of malaria parasites. This allows researchers to treat them before they become ill. Researchers can administer trial drugs to monitor their effectiveness, and capture information that can help develop treatments. This enables researchers to know quickly if a drug is suitable for large–scale trials, and provides data to support vaccine development. "It is important that we understand the human biology of the vaccines before we start doing big clinical trials," says Tim Wells, Chief Scientific Officer at Medicines for Malaria Venture. (*Financial Times*, 23 Apr 2015)

▶▶ UNICEF Australia has criticised new cuts to Australia's international aid programmes, which total US$ 800 million. UNICEF and other aid agencies will have to scale–back operations as a result. Australia's contribution to international aid already falls short of the UN's target of 0.7% of GDP. Felicity Weaver, UNICEF Australia's International Programme Manager, says that these cuts are unfair. She cited how the cholera outbreak in Zimbabwe cost 4000 lives, and that US$ 800 000 cuts to a programme to install and manage clean water for small communities in Zimbabwe is risking lives. (*UNICEF Australia*, 13 May 2015)

▶ China

▶▶ A study by New York University and East China Normal University (*Walking, obesity and urban design in China*) uncovers the impact of the built environment on physical activity in six densely–populated areas in Shanghai and Hangzhou. The areas were rated for ease of walking and cycling, including footpaths, trees, benches, street width and kerb cuts; plus barriers to exercise such as pavement and bicycle lane obstructions and air pollution. It found that rates of walking and cycling for recreation and commuting are higher in areas with fewer impediments. Although the results may be unsurprising, they could be crucial in persuading local government officials and developers of the benefits of more walkable urban development patterns – at a time of high and increasing rates of obesity and chronic diseases in Chinese cities. (*Cities Today*, 3 Mar 2015)

▶▶ China has set out a roadmap for fixing its health care system, which is plagued by queues and poor rural services. China's State Council announced plans to double the number of general doctors to two per 1000 people by 2020, and increase the numbers of nurses and support staff. It will also investigate using technology such as mobile devices and online cloud systems to support these changes, and introduce databases for electronic health records and expand patient information records across the entire population. It will speed up the development of grassroots health care, and may further open up health care to the private sector. China's health care market will be worth an estimated US$ 1 trillion by 2020, making is highly lucrative for drug manufacturers, medical device firms and hospital operators. (*Reuters*, 31 Mar 2015)

▶▶ Lao People's Democratic Republic began a GAVI–supported campaign to vaccinate its children about Japanese Encephalitis (JE). This campaign marks the first time GAVI has provided support to a Chinese–manufactured vaccine – made possible by WHO's decision to pre–qualify the vaccine produced by the Chengdu Institute of Biological Product. This is the first time a Chinese manufacturer has achieved this standard. JE, a vaccine–preventable disease, is mosquito–borne with no specific treatment – and can lead to severe disability or death. Each year, there are 70 000 cases of JE, and 20 000 resulting deaths. WHO estimates that 3 billion people in Asia are at risk of JE, and 24 countries have endemic transmission. (*Financial Express*, 1 Apr 2015)

▶▶ Alibaba Groups Holdings is expanding into China's booming online health care markets. It announced a US$ 2.5 billion deal to move its web pharmacy business into its

publicly listed health division. This will enable the group to move into the sale of prescription drugs if regulations change, and places it to cater to an aging, wealthier population wrestling with chronic conditions (eg, heart disease, diabetes), that is more interested in health products and monitoring. Expanding China's online drug sales could reshape its US$ 149 billion pharmaceuticals market by moving sales online away from hospitals, and its fragmented pharmaceutical supply chain offer further opportunities for efficiency gains. (*bloomberg.com*, 15 Apr 2015)

▶▶ The Hong Kong government has proposed new regulations on the nutrition and health claims on infant formula milk, aiming to increase breast–feeding rates. To date, Hong Kong has been lax in allowing manufacturers to make misleading claims on the benefits of formula–feeding, which may cause some mothers to believe that formula milk is better than breast milk. The WHO recommends breastfeeding for at least the first six months of a child's life. The government has yet to decide whether to ban all nutrient and health claims, or whether to allow some health claims. Manufacturers' associations are campaigning for more flexibility, whilst breastfeeding campaigners argue for a more restrictive approach. Any restriction would apply to infant formula, follow–up formula and pre–packaged food for children aged under 36 months. (*South China Morning Post*, 17 Apr 2015)

▶ Europe

▶▶ Cancer Research UK forecasts that 1–in–2 people in the UK will be diagnosed with cancer at some point in their lives – an increase from its earlier estimate of 1–in–3 people. Increased life–expectancies, and fewer deaths from infections and heart disease mean that more people are living long enough to develop cancer. However, cancer survival rates are increasing, and improving lifestyle (eg, losing weight and stopping smoking) have major benefits. Breast and prostate cancers are likely to remain the most common, although head and neck cancers (caused by the human papillomavirus) and tumours in the food pipe (linked to acid reflux causes by obesity) are becoming more common. Sean Duffy, the national clinical director for cancer at NHS England, calls for improved prevention, faster diagnosis, better treatment, and care and after–care for all patients. (*BBC News*, 4 Feb 2015)

▶▶ A study of 26 European countries, published in the *BJOG: An International Journal of Obstetrics & Gynaecology*, found wide variations in Caesarean section (C–section) rates across Europe. Rates are 17% in Sweden, 25% in the UK and 52% in Cyprus. It found that C–section rates have risen in most EU countries, although may be levelling off in some countries. C–sections are safe procedures, albeit riskier than vaginal births. Reasons behind this increase may include a fear of litigation, financial incentives, maternal requests, and the belief that it is a safe procedure. Prof. Alison Macfarlane, professor of perinatal health at City University London said "given that people are supposed to be practicing according to evidence, it is surprising there is such wide variations between countries," and called for further research to ensure that clinical practice is based on evidence. (*BBC*, 9 Mar 2015)

▶▶ Overall, cases of TB in Europe and Central Asia fell by 5.6% between 2012 and 2013, although prevalence is still high in certain countries, and globally the region is the most affected by multi–resistance TB. In 2013, the region had 360 000 reported cases of TB, with 85% occurring in 18 "high priority" countries in Eastern Europe and Central Asia (eg, Romania, Turkey, Kazakhstan, Russia etc.). The incidence of TB is higher where national incomes are lower, and/or where income inequalities are higher. Europe will not be free of TB this century at the current rate of eradication, and the WHO calls for governments to scale up access to effective treatments, and improve diagnosis and care. TB is the second most deadly infectious disease after AIDS, with 1.5 million deaths in 2013 compared to 1.6 million AIDS–related deaths in 2012. (*AFP*, 17 Mar 2015)

▶▶ In an open letter to the WHO Regional Office for Europe, the European Public Health Alliance (EPHA) states its strong support for the WHO's nutrient profile model. It recognises the model as an invaluable tool in identifying foods high in fat, salt and sugar (HFSS), which will curb the marketing of unhealthy foodstuffs to children and ultimately decrease child obesity. EPHA states that voluntary action is inadequate to control the marketing of HFSS food and beverages to children due to wide variations in practice and compliance, and calls for formal regulation. (*EPHA*, 14 Apr 2015)

▶▶ The UN's Sustainable Development Solutions Network shows that Switzerland tops its World Happiness index, closely followed by Iceland, Denmark, Norway and Canada. The World Happiness Report, which aims to influence government policy, bases its rankings on variables such as real GDP per capita, healthy life expectancy, corruption levels and social freedoms. It found the least happy countries were Togo, Burundi, Syria, Benin and Rwanda. (*BBC News*, 24 Apr 2015)

▶ India

India's human development lags behinds its economic development, illustrated by having one of the highest rate of infant deaths in the world – three times higher than China. It spends just over 1% of GDP on publicly–funded health care, compared to 2.9% in China and 4.1% in Brazil, and every year 60 million Indian people are pushed into poverty due to health care costs. The government is designing a National Health Assurance Mission to provide universal health care. To succeed, it must increase expenditure from US$ 20 billion to US$ 45 billion, focusing on high impact investments that could bring India's rate of preventable infectious, maternal and child deaths in line with other middle–income countries, eg, China, Cuba etc. India must expand the use of current medicines, vaccines and diagnostic tests, invest in maternal, newborn and child health, immunisations, malaria control, health–systems strengthening and tackling TB. Action such as tobacco taxation is also needed to tackle non–communicable diseases. The economic payoff would be vast – an estimated US$ 10 for every US$ 1 invested. (*The Economic Times India*, 12 Dec 2014)

HIV support groups claim that India's state–run HIV/AIDS programme (National AIDS Control Organisation – NACO) has ran out of critical supplies, leaving tens of thousands of people without access to life–saving drugs. Supplies of testing kits are also at low levels, and there are reports of difficulties in drug users obtaining clean syringes, and high–risk groups obtaining free condoms. NACO has succeeded in reducing new HIV infections from 274 000 in 2000 to 116 000 in 2011, although India has the 3rd highest number of cases in the world with 2.1 million people living with HIV. "People are being left to die on the road because of bureaucratic delays," says Ms Kousalya Periaswamy, founder of the Positive Women Network and one of the first Indian women to openly state her HIV–positive status. (*WSJ*, 12 Feb 2015)

The Institute of Palliative Medicine has extended its community Palliative Care project across Kerala, Tamil Nadu, Puducherry and West Bengal, caring for terminally–ill people who were not receiving care from their communities or medical system. The project uses village–based volunteers who provide care – spanning medical, emotional, spiritual, financial, familial and logistical care – to dying people, as well as fund–raising to support the project's work. Approximately 100 000 volunteers provide sensitive, compassionate and competent care to people with terminal or chronic illnesses. Sivanthi, a volunteer, brings her children on home visits, and says it has instilled a strong feeling of compassion in her children. (*The Epoch Times*, 15 Feb 2015)

India's child health – still poor despite the country's robust economic growth – is a major public health issue. A child raised in India is much more likely to be malnourished than a child from DR Congo, Zimbabwe or Somalia, with poor sanitation and increasing drug–resistant infections affecting nutrition. Another important factor is the relatively poor health of Indian women. More than 90% of adolescent girls are anaemic (a key measure of poor nutrition), and 42% of Indian mothers are underweight, compared to 16.5% in sub–Saharan Africa. Indian children are also smaller than their counterparts in sub–Saharan Africa. This is surprising, as on average, Indian people are wealthier, better educated and have fewer children. However, gender differences in employment, education and status (eg, Indian women will often eat less than other family members) are wider in India, and this plays a part in malnourished mothers and small children. (*New York Times*, 2 Mar 2015)

Each year, 59 000 people die from rabies transmitted by dogs, with developing countries the worst affected. Rabies is a fatal infection which is almost 100% preventable. Most developed countries have eliminated rabies from their dog populations, but rabies is present in domestic dogs in developing countries, and is often poorly controlled. Most deaths occur in Asia and Africa, with India alone accounting for 35% of deaths. This represents an economic cost of US$ 8.6 billion through premature deaths and lost income. The Global Alliance for Rabies Control calls for increased efforts to vaccinate dogs, particularly in low–income countries, and for vaccines for bite victims to be more affordable and more available. (*BBC News*, 17 Apr 2015)

▶ The Americas

The US pharmaceutical company Pfizer announced that it will cut the price of its pneumococcal vaccine Prevenar 13 by 6% to US$ 3.10/dose in poor countries, as part of its commitment to the GAVI global vaccines alliance. This reduction will continue to 2025, safeguarding access against economic growth in developing countries. This announce-

ment came ahead of GAVI's fundraising conference in Berlin, where it hoped to raise US$ 7.5 billion to extend immunisation in the developing world between 2015 and 2020. GlaxoSmithKline also extended its price–freeze commitment by 10 years for countries moving on from GAVI support, and Sanofi agreed to increase production of yellow fever vaccines to address severe shortages. (*Yahoo news*, 26 Jan 2015)

▸▸ Harvoni, a drug treatment for Hepatitis C manufactured by Gilead Science, is symbolic of US resentment against expensive drugs, whilst US health care funders take a tougher stance towards cost containment. President Obama's Affordable Care Act creates incentives to control costs, although direct government intervention is barred. This could cause the US to more aggressively contain spiralling health care costs, of which prescription medicines account for 10% (and rising). The US's lack of a central mechanism for setting drug prices means that companies charge what the market will bear. However, they argue that this allows them to cover the costs of developing new treatments – with only 4.6% of the world's population, the US has 33% of global drugs expenditure. Brazil, China, Europe and Japan are all trying to limit costs, and India is issuing patent challenges against western pharmaceutical companies. If other countries reject higher prices, reductions in US prices can only come from industry profit margins – although some commentators believe there is ample scope for this. (*Financial Times*, 10 Feb 2015)

▸▸ Globally, the Caribbean is one of the regions most affected by HIV, with adult HIV prevalence about 1% higher than any other region except sub–Saharan Africa. Unprotected sex, both heterosexual and between men who have sex with men, are the main routes of transmission, and rates are also high amongst injecting drug users and sex workers. However, stigma and discrimination faced by people infected with HIV drives the epidemic underground, making it difficult to reach many groups. The Antigua and Barbuda HIV/AIDS Network (ABHAN) has a peer/buddy scheme, which recruits, monitors and retains

patients into treatment programmes. This had led to decreased risky behaviour and improved health. "Many individuals are reluctant to start treatment because of the myths and stories about HIV and AIDS" says Eleanor Frederick, ABHAN's director, also stating that equity and social justice are very important in the HIV response. (*IPS*, 10 Feb 2015)

▸▸ The Puerto Rican Senator, Gilberto Rodriguez, has tabled a bill that would fine parents of obese children up to US$ 800 in an attempt to curb obesity. Children identified as obese will be referred to health advisers to determine the cause of obesity, develop diet and exercise plans with monthly follow–ups. If obesity persists, the parents could be fined up to US$ 500 initially, rising to US$ 800 if there are no improvements. Rebecca Puhl (Rudd Center for Food Policy and Obesity at the University of Connecticut) criticised the proposal for being unfair, an over-simplification of a complex issue and "inappropriately penalises and stigmatises parents." She states that policies which support parents (eg, improved opportunities for physical activity, more incentives to buy healthier food) are more helpful. (*Yahoo news*, 11 Feb 2015)

▸▸ The Americas became the first WHO region to eliminate rubella, and the European Region hopes to follow next. Rubella normally produces mild symptoms in children and adults, but it is devastating to foetuses in the first trimester of pregnancy – globally, 120 000 children are born each year with severe birth defects caused by rubella. Rubella is normally prevented by a triple vaccine against measles, mumps and rubella. Endemic measles were eliminated from the hemisphere in 2002, but imported cases have appeared in pockets of unvaccinated children, partly because some parents who believe that the triple vaccine is linked to autism prevent their children receiving it. However, rubella is less contagious than measles, and its vaccine is more effective, so the rare imported cases have not spread so rapidly. "Now with rubella under our belt, we need to roll up our sleeves and finish the job of eliminating measles as well," says PAHO Director, Dr Carissa Etienne. (*New York Times*, 29 Apr 2015)

▶ The Bill and Melinda Gates Foundation

▶▶ Bill and Melinda Gates' annual letter, published in January 2015, outlined their hopes for the next 15 years. It contained some far–reaching predictions on public health, where they predict by 2030 four more diseases will join smallpox as being completely eradicated. The most likely candidates are polio, Guinea worm, elephantiasis, river blindness and blinding trachoma. "The drugs that can stop these scourges are now being donated in huge numbers by pharmaceutical companies, and they're being used more strategically thanks to advances in digital maps that show where diseases are most prevalent," the letter states. (*Business Insider*, 22 Jan 2015)

▶▶ Bill Gates praised aid efforts to countries affected by Ebola, but warned that the response would have been inadequate had Ebola been more infectious. Now that the epidemic appears to be abating, he calls for countries and aid agencies to "respond faster" by ensuring that volunteer lists are available quickly, and using experimental drugs at an earlier stage to counteract other, potentially more infectious, pathogens. He also announced the new "Global Citizen" social network for volunteers and activists to become more involved in the fight against global poverty. (*Financial Times*, 22 Jan 2015)

▶▶ The BMGF pledged to invest US$ 52 million in the German biopharmaceutical company CureVac. CureVac will use this investment to develop its proprietary mRNA platform, and to collaborate on the development of vaccines for diseases which disproportionately affect poorer countries. CureVac is investigating the use of mRNA as a data carrier to instruct the human body to produce its own proteins to fight diseases. The technology can potentially allow for the rapid and cost–effective production of multiple drugs and vaccines which are thermo–stable – eliminating the need for cold storage and making them more suitable for developing countries. The agreement's terms mean that CureVac must set an affordable price for any BMGF–funded products in developing countries. (*European Biotechnology News*, 10 Mar 2015)

▶▶ In an editorial published in the *New England Journal of Medicine*, Bill Gates warns that the world must learn from the lessons of Ebola, as the crisis fades from attention. Inadequate basic preparation caused delays in combating Ebola, which could be catastrophic if there is an outbreak of a more dangerous disease. He calls for a global warning and response system for outbreaks, coordinated by a sufficiently empowered and funded global institution. Such a system should: enable speedy global decision making; increase R&D investment and clarify regulatory pathways; improve early warning and detection systems; involve trained staff and volunteers; strengthen health systems in low– and middle–income countries; and incorporate preparedness exercises to identify shortcomings. (*New England Journal of Medicine*, 18 Mar 2015)

▶▶ Bloomberg Philanthropies and the BMGF have launched a global fund to help developing countries fight legal challenges to their smoking laws by the tobacco industry. It was launched to counteract the industry's apparent moves to block anti–smoking legislation in developing countries – who often lack resources to defend legal challenges. Health experts claim this has gathered speed as smoking rates fall in developed countries, and the industry seeks to maintain its hold in developing countries – home to 75% of the world's smokers. The fund, administered by the Campaign for Tobacco–Free Kids, will also help countries to draft tobacco legislation that will avoid legal challenges. Tobacco companies say that there are few active cases, and it is routine to give a legal opinion when interests are affected by a proposed law. (*New York Times*, 18 Mar 2015)

▶ The GAVI Alliance

▶▶ In a bid to spur development of an Ebola vaccine, GAVI has committed US$ 300 million to buy the vaccine (conditional upon WHO recommendation), and may spend another US$ 90 million to offer immunisation. The Ebola outbreak has led to debates on the lack of treatment options, and the need to encourage the pharmaceutical industry – wary of investing in Ebola treatments due to limited commercial opportunities – to commit more to develop therapies for tropical diseases. This has been consistently highlighted by the WHO, and in another response, the US government will offer immunity against any legal claims relating to the development and roll–out of three Ebola vaccinations under development. (*Wall Street Journal*, 12 Dec 2014)

▶▶ GAVI's fund–raising campaign to buy 2.7 billion vaccine doses against diseases such as diphtheria, diarrhoea and polio is being undermined by the strength of the US

dollar and the surging Swiss franc. It had set a target of raising US$ 7.5 billion to purchase these doses, but these unforeseen exchange rate movements, which occurred after its initial requests, mean that it may not be able to buy the full amount of doses. The dollar has strengthened against most currencies since summer 2014, making eg, pledges made in euros less valuable. For example, GAVI buys many vaccines from pharmaceutical firms in Switzerland, and the surging Swiss franc (which occurred after the Swiss central bank stopped pegging it to the euro) has serious implications for GAVI's plans. GAVI will negotiate with the pharmaceutical companies if it faces a shortfall. (*The Guardian*, 23 Jan 2015)

▶▶ The US pharmaceutical company Pfizer announced that it will cut the price of its pneumococcal vaccine Prevenar 13 by 6% to US$ 3.10/dose in poor countries, as part of its commitment to the GAVI global vaccines alliance. This reduction will last until 2025, safeguarding access against economic growth in developing countries. This announcement came ahead of GAVI's fundraising conference in Berlin, where it hoped to raise US$ 7.5 billion to extend immunisation in the developing world between 2015 and 2020. GlaxoSmithKline also extended its price–freeze commitment by 10 years for countries moving on from GAVI support, and Sanofi agreed to increase production of yellow fever vaccines to address severe shortages. (*Yahoo news*, 26 Jan 2015)

▶▶ Bangladesh will introduce two new vaccines into its national immunization programme, with the support of GAVI, UNICEF, WHO and the Global Polio Eradication Initiative. More than 3 million children will receive the pneumococcal vaccine, which protects against the one of the main causes of pneumonia, and the Inactivated Polio Vaccine (IPV). Pneumonia is a major killer in Bangladesh, causing 22% of deaths in children aged under 5 years, and introduction of the vaccine will have a major impact on child mortality. Introducing IPV to routine immunisation will further improve immunity and reduce risks associated with vaccine–derived polioviruses. (*GAVI*, 20 Mar 2015)

▶▶ For the first time, deaths caused by cervical cancer are set to outstrip deaths from childbirth. This is partly because the number of women dying in childbirth has fallen by nearly 50% since 1990, to 289 000 per year. At the same times, deaths from cervical cancer have risen to 266 000 per year – a 40% increase. Anuradha Gupta, the Deputy CEO of GAVI, states that these deaths are almost entirely preventable by HPV vaccines, screening and treatment. However, almost 90% of deaths from cervical cancer occur in developing countries with scarce screening and treatment services. GAVI has worked with manufacturers to reduce HPV vaccines prices to US$ 4.50 per dose, which will extend coverage across 27 countries. Cancer prevention is much more efficient than treatment, and cervical cancer strikes younger, economically–active women – devastating and impoverishing families. (*Project Syndicate*, 14 Apr 2015)

▶ The World Bank

▶▶ A global coalition, spearheaded by the World Bank, Rockefeller Foundation and WHO, is campaigning for greater progress towards universal health coverage (UHC). Launching on 12 Dec 2014, it highlighted UHC's role in saving lives, ending extreme poverty, building resilience against climate change and ending deadly epidemics. This marks the second anniversary of the UN's resolution which endorsed UHC as a pillar of sustainable development and global security. Each year, 100 million people fall into poverty because of health care costs, and 1 billion people cannot access health care – so disease outbreaks can become epidemics. More low– and middle–income countries are moving towards UHC, recognising that it can protect and improve lives. Knowledge and technologies exist to save and improve lives, but their impact is limited when health care access is limited. (*UHC*, 12 Dec 2014)

▶▶ The World Bank report *The Economic Impact of Ebola on Sub–Saharan Africa: Updated Estimates for 2015* quantifies Ebola's economic impact. It found that Ebola caused economic growth for 2014 in Guinea to fall from 4.5% to 0.5%, from 5.9% to 2.2% in Liberia and from 11.3% to 4% in Sierra Leone. Cumulatively, this represents US$ 0.5 billion – nearly 5% of these countries' GDP. The Bank slashed its 2015 growth forecasts for these countries, to –0.2% for Guinea, 3% for Liberia and –2.0% for Sierra Leone – representing a GDP loss of US$ 1 640 million – more than 12% of their combined GDP. The region is now experiencing wide–spread food insecurity and unemployment. However, the economic impact elsewhere in Africa was limited by the swift response in averting potential outbreaks. The report calls for the speedy elimination of Ebola, and for improved readiness to avoid the human and economic costs of pandemics. (*World Bank*, 20 Jan 2015)

▶▶ The World Bank is working with the UN, IMF and regional development banks on a new pandemic emergency facility to incentivise poor countries' readiness for epidemics, and allow for prompt support to countries in crisis. It

draws upon three financial elements. First, the existing International Bank for Reconstruction and Development, which provides loans, guarantees and risk management products to low– and middle–income countries. Second, the public contingent funding facility, which provides funding to more developed countries, and facilitates speedy crisis management. Third, a new market–based insurance mechanism is under development. Countries would fulfill their obligations by ensuring stronger health systems and being more prepared for an outbreak, whilst insurers have an incentive to work towards disease prevention. The mechanism includes a plan for tackling future major disease outbreaks, expanding laboratory and drug coverage, and increasing the numbers of health workers, and may be available later in 2015. (*Public Finance International*, 10 Mar 2015)

▶▶ According to the World Bank economist Christoph Lakner, the ten richest African people have more wealth (worth US$ 62 billion) than the poorest 50% of Africa's population (worth US$ 59 billion). Similar calculations for India shows that the poorest 50% of its population own the same wealth as the wealthiest 22 individuals; and in

China the richest 5 individuals own the same wealth as the poorest 10% of the population – this would cover more than 40% of the poorest African people. (*World Bank Blog*, 11 Mar 2015)

▶▶ The UK's Overseas Development Institute (ODI) report *The Data Revolution: Finding the Missing Millions* warns that millions more people could be living in extreme poverty than previously estimated. Due to inadequate data collection, the World Bank estimate of 1.01 billion people living in extreme poverty – defined as living on US$ 1.25/day – could be 25% higher. This means that the number of estimated maternal deaths could be inaccurate, and it is unknown how many people are living in cities, how many girls are married before the age of 18 years, etc. It is impossible to tackle poverty and meet development goals without accurate data, but the authors believe that opening up the World Bank's database on income distribution, developing new technologies to allow data to be more readily available, and more investment in data collection and analysis would improve data sources. These methods are needed to help the world's poorest, they conclude. (*The Guardian*, 1 Apr 2015)

▶ United Nations (UN)

▶▶ UNHCR, the UN refugee agency, reports that fighting in eastern Ukraine's Donetsk region is creating new displacement, and nearly 1 million people are internal refugees – set to increase as more people are registered. In addition, 600 000 Ukrainians have been displaced to neighbouring countries, eg, Moldova, Poland and Romania, since Feb 2014. Fighting in the Donetsk region has led to the destruction of buildings, infrastructure and basic services. Many recently–displaced people arrive with few belongings and without proper winter clothes. The UNHCR is working with partners to distribute relief such as clothing and bedding. The UNHCR states that the lack of access to public services is exacerbating an already desperate situation, and calls on all parties to refrain from actions that might endanger civilians, and to adhere to international humanitarian law. (*UNHCR*, 6 Feb 2015)

▶▶ It is difficult to define and measure sustainable development, so UN negotiators have a difficult task in specifying indicators for the Sustainable Development Goals (SDGs) before they are finalised in Sept 2015. There are four key challenges in ensuring that the goals are measurable in a way that sets out a globally sustainable future. First, there are 17 draft goals and 100 indicators but it is unclear who will provide data to monitor and manage their implementation. Second, international bodies and countries need a scientific

method for including innovative data sources (eg, mapping technologies) into SDG monitoring and evaluation. Third, there are too many data categories and indicators, eg, transport access indicators do not capture economic, pollution and climate costs. Lastly, there are frequent gaps between what science measures and how policy is designed, eg, air quality indices may communicate risk but not identify steps to improve air quality. (*SciDev.net*, 11 Feb 2015)

▶▶ At the UN's Commission on the Status of Women, delegates adopted a declaration that confirmed their commitment to achieving gender equality by 2030. However, women's rights and feminist groups argue that the declaration did not go far enough towards the transformative agenda needed to achieve gender equality. The executive director of UN Women, Phumzile Mlambo–Ngcuka, stated that progress has been slow, with "serious stagnation and even regression in some areas." According to UN Women, it will take more than 80 years to achieve economic gender parity, and 50 years to achieve parliamentary gender parity at the current rate of progress. Indigenous women, women with disabilities and women marginalised due to their sexual orientation must be better served by their governments said Mlambo–Ngcuka, adding that substantial steps towards gender equality must be evident within the next 5 years. (*The Guardian*, 10 Mar 2015)

NEWS

▶▶ US$ 4 billion has been pledged in humanitarian aid for Syrians, but the UN says this is less than half the amount needed to help those affected by the war. The UN asked for US$ 8.4 billion (US$ 2.9 billion for those inside Syria, and US$ 5.5 billion for those who have fled to other countries). The UN secretary–general, Ban Ki–moon, described the war in Syria as "the worst humanitarian crisis of our time." Oxfam, the international aid agency, has criticised the "inadequate" international response to the crisis. In addition, the UN's Financial Tracking Service said in November 2015 that nearly 25% of the previous year's pledges (US$ 585 million) are unfulfilled. (*The Guardian*, 31 March 2015)

▶▶ In 2014, 3 300 migrants died attempting to enter Europe, with most drowning in the Mediterranean Sea. 2015 is likely to be worse – according to the UNHCR 60 000 people have crossed the Mediterranean Sea thus far, and 1800 have died. Migrants are fleeing poverty, inequality, climate change, conflicts and human rights violations in Africa and the Middle East. Federica Mogherini, the High Representative of the European Union for Foreign Affairs, called on the international community Security Council to end the crisis and dismantle the people–smuggling networks that support it. Mogherini states that these crossings are security as well as humanitarian crises, as smuggling networks are linked to finance and terrorist activities. The EU is calling for a UN resolution to disrupt networks and destroy boats before their use. The UN Secretary–General Ban Ki–moon rejected a military operation as "potentially dangerous for migrants and local fishermen." (*IPS*, 11 May 2015)

UN AIDS and The Global Fund

▶▶ 34 nations have adopted the target of eliminating malaria by 2030, with an estimated cost of US$ 8.5 billion. This estimate may be revised if disease control measures change due to response to developments, such as increasing drug and insecticide resistance. This estimate comes ahead of the launch of the WHO's global strategy for tackling malaria, and ongoing discussions on including malaria as a target in the post 2015 Sustainable Development Goals. According to the WHO, eight countries have eliminated malaria since 2000. However, global aid for malaria has levelled off, and there has been a 20% reduction in funding for these 34 countries from the Global Fund as it focuses more on higher–burden, lower–income countries. (*scidev.net*, 15 Jan 2015)

▶▶ Nigeria has passed the HIV and AIDS Anti–Discrimination Act 2014, in a move to tackle stigmatisation and discrimination against people living with HIV. As well as preventing discrimination, the legislation enables access to health care and other services, and the protection of the human rights and dignity of HIV–positive people. The UNAIDS Country Director for Nigeria, Dr Bilali Camara, welcomed the legislation, and stated UNAIDS's commitment to working with the government to support its implementation. It is part of Nigeria's wider efforts to end the HIV epidemic by 2030, which has seen a 35% reduction in the number of new HIV infections by 2013. Measures include testing 4 million pregnant women and 8.2 million adults in the past four years, and expanding the number of sites providing services to prevent mother–to–child transmission from 675 in 2010 to 5 622 in 2013. (*NACA*, 2 Feb 2015)

▶▶ The Global Fund has awarded the pharmaceutical company Cipla a US$ 189 million tender for ARV drugs to treat HIV/AIDS. This would enable the drugs – which will be manufactured in India – to be supplied to over 140 countries. Cipla has been associated with the Global Fund since 2002, when it was awarded a long–term contract for supplying anti–malarial drugs. The Global Fund has supported 7.3 million people accessing ARV therapy for HIV, has tested and treated 12.3 million people for TB, and has distributed 450 million mosquito nets to protect against malaria. (*Economic Times India*, 13 Feb 2015)

▶▶ UNAIDS welcomed Belarus's confirmation that it imposes no restrictions on the entry, stay and residence for HIV–positive people, and that foreign nationals will have equal access to health services, including HIV treatment. This announcement brings Belarus's HIV–related laws and policies into alignment with international public health and human rights standards. This moves leaves only three countries in eastern Europe and central Asia with HIV–related travel restrictions. There is no evidence that such restrictions protect public health or prevent HIV transmission. They have no economic justification as HIV–positive people can lead long and productive working lives. "In Belarus and elsewhere, freedom of movement is a right for everyone to enjoy, regardless of HIV status," says UNAIDS Executive Director Michel Sidibé. He also urged for the lifting of such restrictions in the remaining 37 countries, territories and areas where they still apply. (*UNAIDS*, 9 Apr 2015)

▶▶ The "low bono" financial model is being deployed the Global Fund to leverage more support from the private sector. Under a "low bono" arrangement, a company charges

a below–market rate for a product or service – which can be sufficient to generate sustainability, and is not regarded as a charitable donation. The Global Fund has also created an innovation hub to bring together private sector partners to tackle challenges relating to supply chains, financial and risk management, and programme quality. New financial models are critical for funding the Sustainable Development Goals, and banks could also play a crucial role in capacity building and product development eg, in microfinance. (*Devex*, 15 Apr 2015)

▶ UNICEF

▶▶ *Sure Chill*, a small UK company located in a remote area of Wales, has designed a fridge that can run for 35+ days without electricity. Its main aim is to protect vaccines from damage caused by patchy refrigeration, *en route* from the factory to remote clinics. It cools via a water–filled chamber with a block of ice on top, providing stable and energy–efficient temperatures that can be made with sporadic or solar power supplies. *Sure Chill* made more than 1000 fridges in 2014, supplying 45 countries – and customers include UNICEF. It is nearing WHO approval for its longest–lasting cooler. Peter Saunders, *Sure Chill*'s chairman, states that the Ebola epidemic highlights the urgency of improving global health infrastructure. The BMGF is a major investor in *Sure Chill*, giving more than US$ 1 million to help develop the coolers. (*Financial Times*, 9 Jan 2015)

▶▶ According to UNICEF, 14 million children are suffering hardship and trauma as a result of the war in Syria and Iraq, as it highlights the needs of children struggling to cope with violence and the global danger of failing to help a generation preyed on by extremist groups. A report from humanitarian agencies showed that the warring factions have ignored demands for access for humanitarian aid, and that the number of children needing aid has increased by one–third in a year, whilst funding for aid agencies has fallen sharply in relation to needs. Islamic State are increasingly recruiting children into active roles. Despite the chaos, UNICEF and other partners have vaccinated 2.9 million children against polio and 840 000 children against measles. However, the UN estimates that 4.8 million people, including 2 million children, are trapped in areas that cannot be reached by aid. It is dangerous to deliver aid across conflict lines, and security forces regularly remove surgical supplies from convoys. UNICEF has sought US$ 815 million to support its work in these countries, but has only raised 10% of that amount. (*New York Times*, 12 Mar 2015)

▶▶ UNICEF and private investors, including UBS and the Children's Investment Fund Foundation have launched a US$ 1 billion independent fund ("The Power of Nutrition") to tackle childhood and maternal malnutrition in some of the world's poorest countries. It will focus on programmes that cover that first 1000 days of life, from maternal nutri-

tion at conception to a child's nutrition before s/he reaches school age. UNICEF estimates that 161 million children have stunted development due to poor nutrition – and under–nutrition contributes to 45% of deaths in children aged under 5 years. Properly nourished children are 33% more likely to escape poverty as adults. Sri Mulyani Indrawati of the World Bank called under–nutrition one of the world's "most serious but least addressed" public health problems. "Getting children the right nutrients at the right time can save 3 million lives and make sure that children keep up in school and become productive adults." (*USA Today*, 16 Apr 2015)

▶▶ In light of tragedies on the Mediterranean Sea, where hundreds of men, women and children are dead or missing, UNICEF calls for all actions to be guided in the best interests of children. Children who survive these crossings are often placed in unsafe and unsuitable conditions, and may be criminalised. This is in violation of the Convention of the Rights of the Child. UNICEF calls for children to be cared for in a safe place – not a detention facility – with access to education, health, social and legal services and full implementation of existing safeguards. The numbers attempting this crossing will increase as summer approaches, and more senseless deaths could happen unless decisive action is taken. This includes following the EU's existing safeguards for unaccompanied minors, and tackling the root causes of migration in the countries of origin – violence, poverty and discrimination – to avoid more tragedies. (*UNICEF*, 20 Apr 2015)

▶▶ Ahead of the 2015 World Immunisation Week, UNICEF praised China's achievement in vaccinating millions of children, and called for all children to be vaccinated. An estimated 20% of children miss basic, life–saving, vaccinations, and the World Immunisation Week appeals for the poorest and most marginalised children to be reached. China's Expanded Programme on Immunisation has contributed to steep falls in deaths and disability from preventable diseases (eg, polio, diphtheria and meningitis), and its reaching the MDG of reducing mortality in children under 5 years. Failure to vaccinate groups of children can cause outbreaks of preventable diseases that threaten all children. Therefore, this year's focus includes dispelling some of the

myths surrounding vaccination. UNICEF calls for all governments to provide adequate funding for vaccination, and to make it an essential part of universal health coverage.

China has committed US$ 5 million to GAVI to support vaccination in the poorest parts of the world. (*UNICEF/ Women of China*, 27 Apr 2015)

▶ World Health Organization (WHO)

▶▶ Dr Margaret Chan, the WHO director–general, announced that she would like all tobacco companies to be shut down. Speaking at the World Conference on Tobacco and Health in Abu Dhabi, she said that cigarette companies use various tactics to undermine anti–tobacco laws, including political funding. Governments are also being intimidated by industry's litigation threats – although Bill Gates and Michael Bloomberg have announced an anti–tobacco litigation fund to help counteract these threats. However, the WHO notes that globally tobacco use is falling, and non–smoking is becoming the norm. It recommends that governments increase their efforts against industry efforts to buck these trends. (*Voice of America*, 18 March 2015)

▶▶ The WHO launched a network of rapid response medical teams to respond to humanitarian emergencies world–wide. It is appealing to health services and medical aid agencies to register with it, to enable the optimal co–ordination of specialist expertise and knowledge shearing. Dr Ian Norton, who heads the project, said project aims to have suitably qualified teams across the world ready to deploy in the case of major emergencies such as epidemics, earthquakes and tsunamis. "We are asking organisations, countries and NGOs to register. We expect at least 150 to register within the first year," he said. Authorities in countries hit by emergencies will be able to consult the list and decide which foreign medical teams they need. (*AFP*, 8 Apr 2015)

▶▶ In a statement, the WHO admitted to "serious failings" in its handling of the Ebola crisis, and promised reforms to avoid a repeat. The statement listed 8 lessons learned from the outbreak, including improved communications and information–sharing. It is claimed that the WHO's hesitancy in declaring the outbreak an emergency is a major factor behind the epidemic becoming the worst Ebola crisis on record, with more than 25 000 cases and 10 000 deaths. "We have learned lessons of humility. We have seen that

old diseases in new contexts consistently spring new surprises," said the WHO Director–General Margaret Chan. (*Reuters*, 20 April 2015)

▶▶ The WHO has called for the disclosure of all clinical trial results for new drugs, regardless of their success, to increase transparency in the drug innovation process. Many studies show that clinical trial results are never published, especially if they fail to show a beneficial impact – causing research duplication and money being wasted. Lack of access to existing data can hinder the development of drugs and vaccines for developing countries, as trials have to start from scratch and are therefore more expensive – and affects decision–making on international health initiatives. The medical charity Médecins Sans Frontičres (MSF) calls for increased disclosure of results, enforced by law and regulation if necessary. MSF notes that commercial confidentiality is insufficient reason for non–disclosure. "Once a drug or vaccine is registered and on the market, all data can be published," says MSF's Manica Balasegaram. (*scidev.net*, 23 Apr 2015)

▶▶ An independent panel on the WHO response to Ebola states that the crisis could have been prevented if the WHO more quickly sought outside help. The panel was commissioned by WHO and will present its final report in July. The panel is also investigating why early warnings did not lead to an adequate response with international mobilisation and consistent communication strategies, and the delay in declaring Ebola a public–health emergency. The panel highlights the "serious gaps" in handling the outbreak, when traditional burial customs helped spread Ebola, and "bleak" communications reduced communities' willingness to engage. The panel calls for extra investment in the WHO to strengthen its emergency–response capabilities as there is "strong, if not complete, consensus that WHO does not have a robust emergency operations capacity or culture." (*Wall Street Journal*, 11 May 2015)

▶ Demography

▶▶ Globally, the age of marriage is increasing, which translates into lower numbers of child brides. The proportion of young women married before the age of 18 fell from 33% in 1985 to 25% today, and the proportion married before the age of 15 fell from 12% to 8% over the same period. Higher age at marriage tends to reflect more freedom in choosing a spouse, and there is a 40% decline in arranged marriages across Africa and Asia. Increasing education, employment and urbanisation could be factors behind the decline in arranged marriages. Older marriages benefit development, as women are less likely to face violence, or HIV and HPV infections from their partner. Moreover, the mortality risk for young mothers (aged 15–19 years) is twice as high compared to older mothers, and the mortality risk for the infants of young mothers is 73% higher in comparison. (*Bloomberg*, 26 Jan 2015)

▶▶ China's birthrate is one of the lowest amongst developing countries, and a recent change in the law allowed more couples to have a second child. In Shanghai, China's biggest city, 90% of women of child–bearing age are eligible for a second child, but only 5% had applied to do so. An aging society could slow down China's economic boom and strain its pension system, with too few workers supporting growing numbers of elderly people. The governor's office of the populous Shandong province, called attention to another consequence of the country's one–child policy – it has 20% more men than women, as many couples restricted to one child abort female fetuses until they have a male baby. Many Chinese couples are deterred from having more than one child as education and other costs soar, and birth rates have also fallen in neighbouring countries plus Hong Kong and Taiwan. (*The Guardian*, 29 Jan 2015)

▶▶ The world's 300 largest metropolitan economies contribute nearly 50% of global economic output, with only 20% of global population. The Brookings Institution (USA) surveyed the fastest–growing metropolitan areas in 2015, measured by economic performance (including employment and GDP growth). The 10 fastest–growing areas were concentrated in China, Turkey and the Middle East. In China, the cities of Fuzhou, Xiamen, Hangzhou and Kunming were included, based on eg, strong manufacturing, growth in business services etc. In Turkey, Ankara, Bursa, Istanbul and Izmir featured thanks to diversified economies, strong industrial bases and geographical locations. Dubai featured due to its success in diversifying its economy away from commodities towards services. Macau topped the performance index thanks to its strong economic growth, and is now the world's largest gaming centre. (*Brookings Institution*, 10 Feb 2015)

▶▶ In the UK, young adults (aged 20–24 years) have traditionally been wealthier than their elder peers (aged 65–69 years). However, this began to change in 2000–2001, when the living standards of young adults fell, and were overtaken by rising living standards of older adults. The recent recession accelerated this trend, and it is repeated across all socio–economic age groups (albeit more strongly for middle– and low–income families). Rising house prices, which have greatly benefited older people, is one of the main drivers behind this shift. There are few indications that the younger generation is closing the gap, with negative consequences for their financial prospects. Government policies have focused expenditure cuts on working–age rather than pensioner benefits – also sharpening the divide. Angus Hanton of the Intergenerational Foundation calls for government action to redistribute resources more fairly, saying "young people may want to tear up the social contract between generations." (*Financial Times*, 23 Feb 2015)

▶▶ A UK parliamentary report by the Commons International Development Committee (IDC) warns of a "ticking time–bomb" of youth unemployment in developing countries, and globally 600 million young people are competing for 200 million jobs. It states that the problem must be taken as seriously as humanitarian disasters, and it risks widespread social and political unrest. It recommends the UK government's Department for International Development (DfID) widen its focus beyond manufacturing, agriculture and food to include travel and tourism – which could potentially create 73 million jobs by 2025 – and considerable numbers could also be created in health and education. The IDC also says that DfID should have "specific interventions" to help marginalised groups benefit from economic growth, and help lift barriers to women and girls' educational and employment opportunities. (*The Guardian*, 24 Mar 2015)

Economy

▶▶ Growing numbers of South Africans are using digital payment apps rather than cash, and digital payments are becoming more widely accepted by vendors ranging from street traders to large retailers. Digital retailers are driving down costs – many do not charge shoppers a transaction fee, and retailers pay a small fee which is comparable to, or cheaper than, a card transaction fee. More than 50% of South Africans own a mobile phone, so there is a vast potential market for digital payments. Digital payments could expand into other areas, such as church collections and car–parking fees. (*BBC*, 5 Dec 2014)

▶▶ In developing countries, the gender gap in access to formal financial services is great, with women 20% less likely than men to have a bank account. This gap, particularly marked amongst poorer people, impedes women from tapping into market opportunities and widens existing gender imbalances. If financial services are designed around women's needs – convenience, reliability, security, privacy – improved access could lead to greater economic participation, empowerment, account ownership and asset accumulation. Mobile technology can facilitate this by providing services in remote areas, shifting financial decision–making towards women, and making it easier for women to receive remittances from husbands working elsewhere. However, many women do not possess mobile phones or know how to use them, so the products must be simple to use. Governments must also support suitable regulatory environments and remove discriminatory laws that impede women's access to finance. (*OECD*, 6 Feb 2015)

▶▶ Between 2002 and 2013, 60 million people in Latin America moved out of poverty, and the poverty rate – the proportion of people living on less than US$ 4/day – fell. However, progress has stalled since 2013, and the region's poverty rate remains stuck at 28%, whilst the proportion of people in extreme poverty (ie, living on less than US$ 2.50/day) rose slightly to 12%. With a per–person income of US$ 13 500, Latin America is an upper–middle income region, but faces extreme income inequality with large numbers of poor people. Reasons behind this faltering progress include slowing economic growth; less job creation; and poorer people benefiting disproportionately less from existing economic growth. Latin America now faces challenges of implementing more effective mechanisms for helping people out of poverty; and for ensuring that people can leave poverty permanently. Improved economic growth will help, but better policies and investments are needed alongside it. (*The Economist*, 19 Feb 2015)

▶▶ In a speech at the opening of the China Development Forum, Vice Premier Zhang Gaoli said that China will work to unleash new economic growth as China, to maintain a medium–high growth rate and transition to a medium–high development level. The government plans to expand economic reforms to spur growth arising from entrepreneurship, innovation and creativity. It will make China's economy more open to the outside world in order to achieve prosperity and share development opportunities. China is moving away from the double–digit growth of the past decade towards slower but high quality growth – the "new normal". (*Xinhau*, 22 Mar 2015)

▶▶ Demographic changes, the impact of the economic crisis, and the low–growth, low returns and low yields environment is presenting crucial and far–reaching challenges to pension systems of all sorts. The *OECD Pensions Outlook* discusses how these challenges are being addressed. Ageing, due to lower fertility and higher life expectancy, increases a population's average age. This creates problems of adequacy, solvency and financial sustainability. The *Outlook* argues that contributing more, and for longer (eg, by increasing retirement ages) is the best approach. However, this could be unfair if gains in life expectancy are distributed unevenly, and linking the number of years' contribution may be more equitable. Uncertainties over future improvements in mortality and life expectancy can be overcome by transferring the risk to annuity providers (eg, life insurers). Pension funds and annuity providers will need regularly updated mortality tables that incorporate future predictions, based on trends in the relevant population. A regulatory framework that ensures capital markets can mitigate longevity risk, eg, by index–based instruments to hedge risk will also help. (*OECD*, 9 May 2015)

Energy

▶▶ 1.2 billion of the world's poorest people lack mains electricity, and a further 2.5 billion people have inadequate power. Sub–Saharan Africa, with 910 million people, consumes less electricity than Alabama, USA – equivalent to one light bulb per person for 3 hours/d. Without electricity, people rely on paraffin – expensive and dangerous, with

indoor fumes causing 600 000 preventable deaths in Africa alone. However, new technologies are providing potential solutions as Africa's population is set to double by 2040. Solar power is now cheaper to generate, falling from US$ 4/watt in 2008 to US$ 1 in 2014. Light emitting diodes – highly efficient at converting electricity to light – have also fallen in price, and more solar–powered devices and systems are available. Quality, technical and capital constraints curtail wider up–take – although the International Energy Authority estimates that 500 million people without electricity will have at least 200 W/person by 2030 thanks to solar power. (*The Economist*, 15 Jan 2015)

▶▶ Nepal cleared China's Three Gorges International Corp. to build a US$ 1.6 billion hydropower project – its single–biggest foreign investment. The dam will be built on the West Seti River in northern Nepal, and will generate 750 megawatts (MWs) of power upon completion in 2021–2022. Nepal, one of the world's poorest countries, is opening up its vast hydropower potential to ease power shortages and strengthen its war–torn economy. This has led to China and India to invest in Nepal's energy–building, and India has begun exporting energy. Nepal could potentially generate 42 000 MW of hydropower, but currently produces 800 MW – much less than the demand of 1 400 MW. In 2014, Nepal gave clearance to two major India hydropower projects worth a combined US$ 2.4 billion. China is investing in other infrastructure projects, including the road linking the capital Kathmandu with the Tibetan border. (*Reuters*, 13 Apr 2015)

▶▶ Since 2013, the world has added more renewable energy capacity than coal, natural gas and oil combined. According to an analysis presented at the Bloomberg New Energy Finance (BNEF) Summit, this trend will accelerate, and by 2030 more than four times as much renewable capacity will be added – despite recent falls in oil and gas prices. Falling wind and solar prices mean that they are now cheaper, or equivalent to, grid electricity in much of the world, and solar power could be the world's biggest en-

ergy source by 2050. However, BNEF warns that projected investment levels in renewable energy fall short of averting a global temperature increase of 2°C, and hence the most severe consequences of climate change. (*bloomberg.com*, 14 Apr 2015)

▶▶ The European Commission (EC) has sent a Statement of Objections to Gazprom, the Russian state–owned gas company, over its alleged abuse of market power in Central and Eastern Europe gas markets. Gazprom denies these claims. This is part of a wider anti–trust case that was initially opened in August 2012. The EC believes that Gazprom has broken EC anti–trust rules by "pursuing an overall strategy to partition Central and Eastern European gas markets, with the aim of maintaining an unfair pricing policy in several of these member states' by: the possible hindering of cross–border gas sales; alleged unfair pricing policy; and concerns over gas transport infrastructure. However, the EC could be applying its competition policy in under–developed markets, making it difficult to prove market abuses – and unfair pricing practices. Likewise, infrastructure is a government responsibility, not Gazprom's. If the EC complaint is upheld, Gazprom can be fined up to 10% of its annual revenues. (*Brookings Institution*, 23 Apr 2015)

▶▶ According to a report by the International Monetary Fund, energy subsidies – at US$ 4.2 trillion in 2011 – are much higher than previously estimated, and are equivalent to 5.8% of global GDP. These subsidies are set to grow to US$ 5.4 trillion (6.5% of global GDP) by 2015, despite falling energy prices. This is more than is spent on social welfare (estimated at US$ 1.4 trillion, or 2% on global GDP in 2013). High levels of subsidies on environmentally–damaging coal and petroleum energy sources account for a large share in the overall cost. Reforming these subsidies would not only be environmentally beneficial, but would enable expenditure to be re–directed towards social welfare, eg, reducing labour taxes or increase expenditure on education and health. (*International Monetary Fund*, 11 May 2015)

▶ Environment

▶▶ According to the UN World Meteorological Organisation (WMO), 14 out of the 15 hottest years on record have occurred since 2000, with 2014 being the hottest year on record since 1850. The average global air temperature over land and sea in 2014 was 0.57°C above the average of 14°C for the 1961–1990 reference period. The record temperature was above temperatures in 2005 and 2010, albeit within a margin of uncertainty. The WMO secretary–general, Michel Jarraud, expects global warming to

continue due to rising levels of greenhouse gases and the increasing heat content of the world's oceans. The WMO also noted that 2014 temperatures occurred despite a fully–formed El Niño event, which drives up temperatures. The confirmation of 2014's extreme heat comes ahead of the next round of UN climate negotiations in Geneva, which are intended to pave the way towards a global agreement to tackle climate change. (*The Guardian*, 2 Feb 2015)

▶▶ Taiwan experienced its lowest winter and autumn rainfalls since 1947, leading to its worst drought for 70 years. As a result, Taiwan introduced water rationing in some cities to deal with urgent water shortages. Homes, schools and business are reliant on water stored in tanks, and water–saving measures (eg, recycling water, closing swimming pools and gyms), are being adopted. Despite some light rainfall, the government warned that the dry spell is set to continue, and that monsoon rains may not happen this season. (*The Guardian*, 8 Apr 2015)

▶▶ Under international law, people leaving their countries due to natural disasters or environmental degradation are classed as normal migrants, rather than refugees fleeing persecution. This may become more pressing, as one of the effects of climate change will be more frequent, intense and unpredictable natural disasters. The Nansen Initiative was sent up to explore this gap in international law, and highlights how little is known about future migratory patterns. There are widely varying estimates of how many people will move within their countries, or cross national borders as a result of natural disasters and climate change. Uncovering the risk of displacement from these events is complex, as environmental and economic migration can intersect. Elizabeth Ferris, Co–Director of the Brookings/LSE Project on Internal Displacement, calls for policies and mechanisms that will help those who cannot survive in their own country, and will seek to enter another country. (*Brookings Institute*, 22 Apr 2015)

▶▶ Ahead of a UN summit in Paris on limiting climate change, a new study found that global warming is responsible for 75% of moderate hot extremes and 18% of downpours. 2014 was the warmest year on record since the 19th century, and heavy flooding hit several countries including Serbia, Bangladesh and Morocco. Global average temperatures have risen 0.85°C above pre–industrial levels, and further warming would increase the risk of extremes. The authors warn that a temperature increase of 2°C from pre–industrial times would raise the share of heat extremes attributable to warming to 96%, and the share of extreme rainfall to 40%. (*Yahoo*, 27 Apr 2015)

▶▶ A study published in the journal *Science* outlines threats to soil productivity – and hence food production – arising from soil erosion, nutrient exhaustion, urbanisation and climate change. The soil layer is only 1m thick, and has a critical life–support role. 40% of the planet's terrestrial surface is used for agriculture, whilst other large – and growing – areas are urbanised. As the remaining land is less suitable for cultivation, the study's authors recommend more effective use of current land resources in order to support the world's growing population. Soil is eroding more quickly than production, resulting in the loss of key nutrients and the unsustainable use of chemical fertilisers. "Unless we devise better ways to protect and recycle our soil nutrients and make sure that they are used by crops efficiently rather than being washed away, we are certainly headed for nutrient shortages," says Donald Sparks, one of the report's authors. He also noted that disruptions of food production could become a source of conflict. (*Science Daily*, 7 May 2015)

▶ Food, Water and Sanitation

▶▶ Senegal's capital city, Dakar, will be the test site for the new Omniprocessor technology. The Omniprocessor is a compact waste treatment plant that can process sewage for a community of 100 000 people. Conventional sewage plants use large amount of electricity to process waste, but the Omniprocessor combines incineration, steam power and filtration techniques to ensure no energy is wasted in the process. It also generates 11 000 L of drinking water in the process, and derives enough energy from the faecal matter it incinerates to run the unit, with an additional 150 kw/d to export to the national grid. Its ash can be commercially valuable as a fertiliser. The system's ability to generate revenue will support its running costs – crucial when sewage systems are abandoned when countries cannot afford maintenance. It is a potential weapon in tackling the problem of 2.5 billion people without sanitation – poor sanitation is one of the main reasons behind 1.5 million children

dying each year from diarrhoea. (*The Guardian*, 20 Jan 2015)

▶▶ A report from the Waste and Resources Action Program (WRAP) showed that 60 million tonnes of food is wasted each year in the USA, with an estimated value of US$ 162 billion – and 32 million tonnes end up in landfills, at a cost of US$ 1.5 billion to local governments. This problem is not confined to the USA – it estimates that globally, one–third of food is never consumed, costing up to US$ 400 billion annually. Reducing food waste to 20% could save US$ 120–130 billion a year by 2030, and the UN Food and Agriculture Organization states that food waste by retailers and consumers in developed countries is sufficient to feed the world's 870 million hungry people. Food waste is expected to increase with the growing global population, and this has environmental costs (eg, water and energy usage).

Food landfills also emit methane, a greenhouse gas, so reducing food waste could also reduce global warming. WRAP applauds efforts to reduce food wastage, but calls for more preventative measures. (*New York Times*, 25 Feb 2015)

▶▶ A new report from the WHO and WaterAid shows that globally, 500 000 babies die in their first month of life from preventable deaths in unclean hospitals and clinics. Sepsis is a major killer in the first month, and can be prevented by hand–washing, washing the baby in clean water, and making sure the instrument used to cut the umbilical cord is clean. The report showed that more than one–third of such centres in developing countries lack hand–washing or toilet facilities, and nearly 50% in Africa lack access to clean water. Water supplies, where they exist, are often unreliable and inaccessible. Lack of water and sanitation contributed to the spread of Ebola; with pressures on inadequate health systems from malaria and diarrhoea – both related to, and spread by lack of sanitation – made it more difficult to tackle Ebola effectively. (*Newsweek*, 17 Mar 2015)

▶▶ A UN report published ahead of World Water Day on 22 March states that the world will face a 40% shortfall in water supply by 2030 unless there are major improvements in water management. Overall, demand for water will increase by 55% by 2050. The output from agricultural and manufacturing sectors – both intensive water consumers – will rise due to increasing population. It expressed concern over decreasing groundwater supplies, and the contamination of groundwater by seawater due to rising sea levels. It noted that 748 million people lack access to improved drinking water, with poor people, the disadvantaged and women more likely to be affected. A US$ 53 billion investment – less than 0.1% of global GDP – in water and sanitation could give universal access, and reap substantial economic benefits. It also called for the sustainable development goals to include governance, water quality, wastewater management and the prevention of natural disasters. (*LiveMint*, 20 Mar 2015)

▶▶ At a G20 meeting on food security and nutrition, agriculture ministers stated that food waste is a huge economic problem. Each year, an estimated 1.3 billion tonnes – 30% of global food production – is lost or wasted, which could easily feed the world's 800 million hungry people. The ministers said countries need better estimates of food waste and the economic impact of food loss to help fight the problem. (*The Guardian*, 8 May 2015)

▶ Peace and Human Rights

▶▶ 2014 saw the rise of the Islamic State in Iraq and Syria, Russian forces assaulting Ukrainian borders, civil war in South Sudan and Boko Haram dangerously undermining Nigeria's sovereignty. However, there are signs of hope with Senegal and Nigeria's rapid Ebola response, Lebanon absorbing thousands of Syrian refugees and Afghanistan's marginally–brighter prospects. Out of several countries showing democracy, resilience and potential, *The Economist* identified two main contenders for its Country of the Year – Indonesia and Tunisia. Indonesia's recently–elected reforming president, Joko Widodo, is steering his country towards prosperity. The winner, Tunisia, is a shining exception to the squandered Arab Spring, when it adopted an enlightened constitution and held both parliamentary and presidential polls. *The Economist* lauded Tunisia for its pragmatism and moderation that engender hope in a troubled world. (*The Economist*, 20 Dec 2014)

▶▶ US Senators introduced the End Modern Slavery Initiative Act of 2015, and called for a US$ 1.5 billion fund to combat global slavery through more rigorous law enforcement and prosecution of human traffickers. Slavery and human trafficking and estimated to generate US$ 150 billion profits from the exploitation of 30 million people. The bill aims to cut slavery by 50% over seven years wherever it is most prevalent. The International Justice Mission has documented large reductions in trafficking with modest investments in law enforcement. The Act would authorise the establishment of a non–profit foundation that assists victims, creates preventions programmes and strengthens law enforcement. The US would contribute US$ 251 million in seed money, with an additional US$ 500 million from other governments and US$ 750 million from the private sector. (*Thomson Reuters Foundation*, 25 Feb 2015)

▶▶ The UK–based charity Death Penalty Project (DPP) provides free legal representation by volunteer barristers to people condemned to death around the world. Using "the law to change the law", the DPP campaigns against the death penalty by meticulous objections and reasonable restrictions, and always working within each country's rules. It has saved hundreds of people from executions, making future executions less likely in the process. The DPP has succeeded in having the death penalty declared unconstitutional in Uganda and three Caribbean countries, and mandatory death sentences declared unconstitutional in

Kenya and Malawi. The DPP campaigns to have proper policing recognised as a more effective deterrent than capital punishment, and the stated aim of its founders, Parvais Jabbar and Saul Lahrfreund, is "to put themselves out of jobs". (*Intelligent Life*, 11 Mar 2015)

▶▶ More than two–thirds of Syrian school–age refugees in Lebanon are not attending school, usually because their families cannot afford the fees or because they need to work to support their families. Sometimes, no schools are available, or children lack transport to attend school. It is very difficult for children who miss years of schooling to catch up on their education, and organisations such as World Vision are working to enable more refugee children to attend school. Their programmes include accelerated learning for "out–of–school" children, remedial classes, and informal education. They are also supporting teachers and providing more teaching infrastructure. However, these efforts fall short of what is needed, and a whole generation of children is growing up displaced and uneducated – with real, long–term impacts on them and their country – and providing access to education is something the world should not ignore. (*The Guardian*, 15 Mar 2015)

▶▶ According to the UN, the number of refugees seeking asylum in developed countries is at its highest level for 22 years, rising by nearly 50% in 2014, with an estimated 866 000 asylum seekers lodging claims. The increase is caused by the conflicts in Iraq and Syria, which have created the "worst humanitarian crisis of our era," according to UNHCR spokeswoman Melissa Fleming. These figures do not include Syrian refugees who have been taken in by countries such as Lebanon and Jordan. She urged European countries to open their doors, and respond as generously to the current situation as they did in the Balkan wars in the 1990s. (*BBC*, 28 Mar 2015)

▶ Science and Technology

▶▶ Scientists at the World Economic Forum in Davos called for changes to the development and licensing of new cancer drugs, to enable countries to cope with cancer's increasing burden. Pharmaceutical companies should cut prices in return for a system where promising drugs can be licensed earlier without full–blown and expensive clinical trials, and prices increased if there is sufficient patient benefit. Other countries are looking at the US Food and Drug Administration's breakthrough therapy designation, which accelerates approval of drugs for life–threatening conditions when benefits outweigh risks. Globally, cancer costs US$ 2 trillion a year in lost output and treatment costs – equivalent to 1.5% of global GDP – and pharmaceutical spending doubled to US$ 91 billion in 2013. "The current system for drug discovery and development is failing to deliver enough genuinely innovative advances in treatment, or to produce new drugs at a cost that is affordable for taxpayers," says Paul Workman of the UK's Institute of Cancer Research. (*Financial Times*, 25 Jan 2015)

▶▶ Pharmaceutical companies are accused of restricting access to drug treatments for Hepatitis C in developing countries. Gilead allows cheap copies of its drug sofosbuvir to be made by generic companies and sold in developing countries. However, Médecins Sans Frontiéres (MSF) argue that Gilead is imposing unacceptable conditions in its efforts to ensure that cheap generic copies do not reach developed countries. According to MSF, these conditions – which include requiring patients to prove identification, citizenship and residency – penalise refugees and marginalised groups. Anand Grover, a former UN special rapporteur on the right to health, agrees that these measures are contradictory in improving access to crucial drugs, and arguably, a violation of the right to health. Gilead responded by stating that these measures are designed to prevent the drugs from being diverted from their intended recipients. (*The Guardian*, 20 Mar 2015)

▶▶ According to a study published in the journal *Protein and Cell*, biologists in China have carried out the first experiment to alter the DNA of human embryos, whereby enzymes are introduced that bind to a mutated gene, eg, one associated with disease – and then repair or replace it. There are considerable ethical concerns over such work, as altering the DNA of human sperm, eggs or embryos could produce unknown effects on future generations, as the changes will be passed onto their offspring. This "germline editing" is a separate technology from "germline engineering" which alters the DNA of non–reproductive cells to repair diseased genes. Edward Lanphier (Chief Executive of Sangamo BioSciences Inc, and part of a group of scientists which has called for a global moratorium of such experiments) fears that this call is being ignored, and that it will be "the first of what may be many papers" on human germline engineering. (*Reuters*, 23 Apr 2015)

▶▶ Globally, 44 million people suffer from dementia, and current models of innovation have not delivered effective treatment for them. However, the revolution in digital health data (driven by technological developments, eg,

broadband access, cloud computing and smart phones) could help address this. Dementia is clinically and biologically complex, so the studies required to underpin drug development need massive and diverse data collection, storage and processing. This data are being generated, and harnessing it would have wide–reaching benefits, but researchers' willingness to share data are often constrained by other factors. First, patients' informed consent tends to be limited to the primary study focus, and therefore often excluded for further studies. Step–by–step or dynamic consent models could address this. Second, scientists face disincentives in disclosing data, especially at pre–publication, so action is needed to boost data access and openness. Third, large–scale investment is needed in the necessary big–data infrastructure. Without better data sharing and knowledge co–ordination, there will be limited progress in understanding neurodegenerative diseases and treatments. (*OECD*, 1 May 2015)

▶▶ According to research published in *Science*, the measles vaccination prevents measles–induced immune system damage which makes children more vulnerable to other infectious diseases. The measles pathogen destroys immune system cells which "remember" how to attack other, previously–encountered, pathogens for 28 months after infection. During this time, children are more likely to die from other infections (eg, sepsis, pneumonia, and bronchitis). Prior to the introduction of measles vaccination in developed countries, measles may have been involved in 50% of childhood deaths from infectious diseases. This has important implications for maintaining high levels of measles vaccination, as the benefits are wider– reaching than protection against measles. (*Scientific American*, 7 May 2015)

NEWS

EUGHS news

From this issue onwards, we are adding an additional item to our regular News section – *EUGHS News*. This section will regularly review the activities of our thriving student's society – Edinburgh University Global Health Society (EUGHS) – during the previous semester. In this inaugural section, we will start with reviewing the entire track record of student research projects and publications in global health with Professors Harry Campbell and Igor Rudan and Drs Harish Nair, Evropi Theodoratou, Lina Zgaga, Davies Adeloye and Kit Yee Chan in the period 2006–2015. We will also review students' attendance at International Conferences, their presentations at these conferences, and their internships at the World Health Organization's Headquarters in Geneva, Switzerland, which were arranged and supported through research projects of the above group of researchers and the *Journal of Global Health*.

Following this documentation of all the activities to date, we are bringing two personal accounts from the two EUGHS interns at the World Health Organization in 2014: Rachel Burge and Katy Wong.

Photo: The launch of the *Journal of Global Health* at the World Congress of Epidemiology in Edinburgh, August 2011. From left: Dr Harish Nair, Professor Harry Campbell, Professor Ana Marušić and Professor Igor Rudan.

TRACK RECORD OF EUGHS STUDENT RESEARCH PROJECTS, PUBLICATIONS, PARTICIPATIONS AT INTERNATIONAL CONFERENCES AND INTERNSHIPS AT THE WORLD HEALTH ORGANIZATION

Professors Harry Campbell and Igor Rudan are Joint Directors of the Centre for Global Health Research at the Usher Institute, the University of Edinburgh; Joint Directors of the World Health Organization's Collaborating Centre in Edinburgh; and Joint Editors–in–Chief, "Journal of Global Health". With their narrow team of collaborators in global health epidemiology – Drs Harish Nair, Evropi Theodoratou, Lina Zgaga, Davies Adeloye and Kit Yee Chan – they mentored a larger number of undergraduate students towards research projects such as SSC2, SSC4 and BMedSci. These projects were focused on global health themes and they typically involved a systematic review of the literature on a clinical or public health topic in maternal or child health that filled an existing gap in knowledge. There was usually some choice in the topic to suit the interest of the student. The topic was selected at the start of the SSC2, SSC4 or BMedSci to ensure it was topical and sufficiently novel. The work usually involved some interaction with international collaborators, eg, developing country physicians, international health experts or technical officers from the World Health Organization and UNICEF. The project usually contributed to ongoing international research projects of the group and lead to a paper submitted for publication, in which the students were typically lead authors.

Photo: Editors and EUGHS members at the launch of the *Journal of Global Health* at the World Congress of Epidemiology in Edinburgh, August 2011.

In the period between 2006 and 2015, we managed to publish 57 student publications in international peer–reviewed journals, involving a total of 73 students (as some of their theses contributed to the same publication as spe-

cific components). In 38 of these publications (ie, two–thirds), the contribution of the students was substantial enough to justify lead authorship.

Based on these research results, our students took part in 12 international conferences in global health, where they made 34 oral presentations. These meetings were typically organized by the World Health Organization, The Bill and Melinda Gates Foundation or other leading global health institutions. Having a publication and/or a presentation at an international conference has been helping our students to be successful in their applications for placements and jobs across the UK following their graduation.

Finally, from 2014 we started arranging internships for EUGHS students at the World Health Organization's Headquarters with our collaborators, which we support through *Journal of Global Health*. Six students took part in these internships to date. A complete lists of activities and students is presented in the following sections.

Photo: Several EUGHS members take part at the International Meeting on Maternal and Child Epidemiology Estimates in Dubrovnik, Croatia, in July 2014. Here, photographed with colleagues from the Johns Hopkins University in Baltimore, USA, and London School of Hygiene and Tropical Medicine, UK.

SSC2, SSC4 OR BMEDSCI STUDENT PROJECTS PUBLISHED OR ACCEPTED FOR PUBLICATION 2006–2015

Table 1 presents a complete list of student publications, to the best of our knowledge (and memory). The name

of the contributing student is underlined in each publication.

Table 1. List of EUGHS student publications

Authors	Title	Journal
Wijesingha S, Graham S	Evidence behind the WHO guidelines: hospital care for children. What are the clinical indicators of PCP?	J Trop Pediatr 2007;53:4–7
McCallum AD, Duke T	Evidence behind the WHO guidelines: hospital care for children. Is caffeine useful in the prevention of apnoea of prematurity?	J Trop Pediatr. 2007;53:76–7
Bulteel N, Henderson P	Evidence behind the WHO guidelines: hospital care for children. What are the risks of HIV transmission through breast feeding?	J Trop Pediatr. 2007;53:298–302
Bulteel N, Henderson P	Evidence behind the WHO guidelines: hospital care for children. What are the risks of formula feeding in children of HIV–infected mothers?	J Trop Pediatr. 2007;53:370–3
Best J, Hughes S	Evidence behind the WHO guidelines: hospital care for children. What are the useful clinical features of bacterial meningitis found in infants and children?	J Trop Pediatr. 2008;54:83–86
Woodfield G, Dugdale A	Evidence Behind the who guidelines: hospital care for children. What is the most effective antibiotic regime for chronic suppurative otitis media in children?	J Trop Pediatr. 2008;54:151–6
Woodfield J, Re P, Argent A	Evidence behind the WHO guidelines: hospital care for children. what is the most appropriate anti–microbial treatment for tuberculous meningitis?	J Trop Pediatr. 2008;54:220–4
Thurey J, Molyneux E	Evidence behind the WHO guidelines: hospital care for children. The usefulness of Azole prophylaxis against cryptococcal meningitis in HIV–positive children	J Trop Pediatr. 2008;54:361–3
Chandy E, McCarthy J	Evidence behind the WHO guidelines: hospital care for children. What is the most appropriate treatment for giardiasis?	J Trop Pediatr. 2009;55:5–7

Table 1. Continued

Authors	Title	Journal
Subhi R, Adamson M, Campbell H, Weber M, Smith K, Ashraf H, Berkley J, Bose A, Brent A, Brooks WA, Bruce N, Chisti MJ, Gessner BD, Gyr N, Mwaniki M, Nadjm B, Nokes DJ, Okiro EA, Reyburn H, Sutanto A, Zaman A, Duke T	The burden of hypoxaemia among children in developing countries	Lancet Infect Dis. 2009;9:219–27
Theodoratou E, Johnson S, Jhass A, Madhi SA, Clark A, Boschi–Pinto C, Bhopal S, Rudan I, Campbell H	The effect of *Haemophilus influenzae* type b and pneumococcal conjugate vaccines on childhood pneumonia incidence, severe morbidity and mortality.	Int J Epidemiol. 2010;Suppl 1:i172–85
Theodoratou E, Al–Jilaihawi S, Woodward F, Ferguson J, Jhass A, Balliet M, Kolcic I, Duke T, Rudan I, Campbell H	The effect of case management on childhood pneumonia mortality in developing countries	Int J Epidemiol. 2010;Suppl 1:i155–71
Jabeen A, Theodoratou E, Yakoob MY, Eisele TP, Ferguson J, Jhass A, Rudan I, Campbell H, Black RE, Haider BA, Bhutta ZA	Preventive zinc supplementation on mortality due to diarrhoea, pneumonia and malaria	BMC Public Health. 2011;11 Suppl 3:S23
Calder D, Qazi S	Evidence behind the WHO guidelines: hospital care for children. What is the aetiology of pneumonia in HIV–infected children in developing countries?	J Trop Pediatr. 2009;55:219–24
Ford A, Campbell H, Duke T	Pathogens and treatment of chronic diarrhoea in HIV	J Trop Pediatr. 2009;55:349–55
Higginson D, Theodoratou E, Nair H, Huda T, Zgaga L, Jadhav SS, Omer SB, Rudan I, Campbell H	An evaluation of respiratory administration of measles vaccine for prevention of acute lower respiratory infections in children	BMC Public Health. 2011;11 Suppl 3:S31
Nair H, Verma VR, Theodoratou E, Zgaga L, Huda T, Simões EA, Wright PF, Rudan I, Campbell H	An evaluation of the emerging interventions against respiratory syncytial virus (RSV)–associated acute lower respiratory infections in children	BMC Public Health. 2011;11 Suppl 3:S30
Choudhuri D, Huda T, Theodoratou E, Nair H, Zgaga L, Falconer R, Luksic I, Johnson HL, Zhang JS, El Arifeen S, Nelson CB, Borrow R, Campbell H, Rudan I	An evaluation of emerging vaccines for childhood meningococcal disease	BMC Public Health. 2011;11 Suppl 3:S29
Catto AG, Zgaga L, Theodoratou E, Huda T, Nair H, Arifeen SE, Rudan I, Duke T, Campbell H	An evaluation of oxygen systems for treatment of childhood pneumonia	BMC Public Health. 2011;11 Suppl 3:S28
Webster J, Theodoratou E, Nair H, Seong AC, Zgaga L, Huda T, Johnson HL, Madhi S, Rubens C, Zhang JS, El Arifeen S, Krause R, Jacobs TA, Brooks AW, Campbell H, Rudan I	An evaluation of emerging vaccines for childhood pneumococcal pneumonia	BMC Public Health. 2011;11 Suppl 3:S26
Yakoob MY, Theodoratou E, Jabeen A, Imdad A, Eisele TP, Ferguson J, Jhass A, Rudan I, Campbell H, Black RE, Bhutta ZA	Preventive zinc supplementation in developing countries: impact on mortality and morbidity due to diarrhea, pneumonia and malaria	BMC Public Health. 2011;11 Suppl 3:S23
Jackson SJ, Steer AC, Campbell H	Systematic review: Estimation of global burden of non–suppurative sequelae of upper respiratory tract infection: rheumatic fever and post–streptococcal glomerulonephritis	Trop Med Int Health. 2011;16: 2–11
Campbell A, Rudan I	A systematic review of birth cohort studies in Africa	J Global Health. 2011;1:46–58
McKinnon R, Campbell H	A systematic review of birth cohort studies in Asia	J Global Health. 2011;1:59–71
Waters D, Jawad I, Ahmad A, Lukšić I, Nair H, Zgaga L, Theodoratou E, Rudan I, Zaidi AKM, Campbell H	Aetiology of community–acquired neonatal sepsis in low– and middle–income countries	J Global Health. 2011; 1: 154–170
Velu PP, Gravett CA, Roberts TK, Wagner TA, Zhang JFS, Rubens CE, Gravett MG, Campbell H, Rudan I	Epidemiology and aetiology of maternal bacterial and viral infections in low– and middle–income countries	J Global Health 2011;1:171–88
Roberts T, Gravett CA, Velu PP, Theodoratou E, Wagner TA, Zhang JS, Campbell H, Rubens CE, Gravett MG, Rudan I	Epidemiology and aetiology of maternal parasitic infections in low– and middle–income countries	J Glob Health. 2011;1:189–200
Theodoratou E, Zhang JS, Kolcic I, Davis AM, Bhopal S, Nair H, Chan KY, Liu L, Johnson H, Rudan I, Campbell H	Estimating pneumonia deaths of post–neonatal children in countries of low or no death certification in 2008	PLoS One. 2011;6:e25095
Sivakumaran S, Agakov F, Theodoratou E, Prendergast JG, Zgaga L, Manolio T, Rudan I, McKeigue P, Wilson JF, Campbell H	Abundant pleiotropy in human complex diseases and traits	Am J Hum Genet. 2011;89:607–18
Edmond K, Scott S, Korczak V, Ward C, Theodoratou E, Clark A, Griffiths U, Rudan I, Campbell H	Global and regional estimates of disabling sequelae from pneumonia 1970–2011	PLoS One 2012;7:e31239
Baxter JM	One in a million, or one in thousand: What is the morbidity of rabies in India?	J Glob Health. 2012;2:010303
Herbert LJ, Middleton SI	An estimate of syphilis incidence in Eastern Europe	J Glob Health. 2012;2:010402
Jawad I, Lukšić I, Rafnsson SB	Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality	J Glob Health. 2012;2:010404

Table 1. Continued

Authors	Title	Journal
George–Carey R, Adeloye D, Chan KY, Paul A, Kolčić I, Campbell H, Rudan I	An estimate of the prevalence of dementia in Africa: A systematic analysis	J Glob Health. 2012;2:020401
Waters D, Theodoratou E, Campbell H, Rudan I, Chopra M	Optimizing community case management strategies to achieve equitable reduction of childhood pneumonia mortality: An application of Equitable Impact Sensitive Tool (EQUIST) in five low– and middle–income countries	J Glob Health. 2012;2:020402
Graham A, Adeloye D, Grant L, Theodoratou E, Campbell H	Estimating the incidence of colorectal cancer in Sub–Saharan Africa: A systematic analysis	J Glob Health. 2012;2:020404
Paul A, Adeloye D, George–Carey R, Kolčić I, Grant L, Chan KY	An estimate of the prevalence of epilepsy in Sub–Saharan Africa: A systematic analysis	J Glob Health. 2012;2:020405
Dowman B, Campbell RM, Zgaga L, Adeloye D, Chan KY	Estimating the burden of rheumatoid arthritis in Africa: A systematic analysis	J Glob Health. 2012;2:020406
Theodoratou E, Montazeri Z, Hawken S, Allum GC, Gong J, Tait V, Kirac I, Tazari M, Farrington SM, Demarsh A, Zgaga L, Landry D, Benson HE, Read SH, Rudan I, Tenesa A, Dunlop MG, Campbell H, Little J	Systematic meta-analyses and field synopsis of genetic association studies in colorectal cancer	J Natl Cancer Inst. 2012;104:1433–57
Nair H, Simões EA, Rudan I, et al., Campbell H. for the Severe Pneumonia Working Group (including Hanlon P)	Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis	Lancet. 2013;381:1380–90
Jackson S, Mathews KH, Pulanić D, Falconer R, Rudan I, Campbell H, Nair H	Risk factors for severe acute lower respiratory infections in children: a systematic review and meta–analysis	Croat Med J. 2013;54:110–21
Luksic I, Kearns PK, Scott F, Rudan I, Campbell H, Nair H	Viral aetiology of hospitalized acute lower respiratory infections in children under 5 years of age	Croat Med J. 2013;54:122 –34
Luksic I, Clay S, Falconer R, Pulanić D, Rudan I, Campbell H, Nair H	Effectiveness of seasonal influenza vaccines in children: a systematic review	Croat Med J. 2013;54:135–45
Kokki I, Papana A, Campbell H, Theodoratou E	Estimating the incidence of colorectal cancer in South East Asia	Croat Med J. 2013;54:532–40
Luksic I, Mulic R, Falconer R, Orban M, Sidhu S, Rudan I	Estimating global and regional morbidity from acute bacterial meningitis in children: assessment of the evidence	Croat Med J. 2013;54:510–8
Nair H, Lau ESM, Brooks WA, Seong AC, Theodoratou E, Zgaga L, Huda T, Jadhav SS, Rudan I, Campbell H	An evaluation of the emerging cross–protective vaccines against influenza in children	BMC Public Health. 2013:13 (Suppl 3):S14
Bhopal A, Callender T, Knox AF, Regmi S	Strength in numbers? Grouping, fund allocation and coordination amongst the neglected tropical diseases	J Glob Health. 2013;3:020302
Geldsetzer P, Williams TC, Kirolos A, Mitchell S, Ratcliffe LA, Kohli–Lynch MK, Bischoff EJ, Cameron S, Campbell H	The recognition of and care seeking behaviour for childhood illness in developing countries: a systematic review	PLoS One. 2014; 9:e93427
Cheema A, Adeloye D, Sidhu S, Sridhar D, Chan KY	Urbanization and prevalence of type 2 diabetes in Southern Asia: A systematic analysis	J Glob Health. 2014;4:010404
Lo A, Polsek D, Sidhu S	Estimating the burden of neural tube defects in low– and middle–income countries	J Glob Health. 2014;4:010402
Adeloye D, Basquill C	Estimating the prevalence and awareness rates of hypertension in Africa: a systematic analysis	PLoS One. 2014;9:e104300
Adeloye D, Basquill C, Papana A, Chan KY, Rudan I, Campbell H	An estimate of the prevalence of COPD in Africa: a systematic analysis	COPD. 2015;12:71–81
Adeloye D, Basquill C, Aderemi AV, Thompson JY, Obi FA	An estimate of the prevalence of hypertension in Nigeria: a systematic review and meta–analysis	J Hyperten. 2015;33:230–42
Kennedy ED, Fairfield CJ, Fergusson SJ	A neglected priority? The importance of surgery in tackling global health inequalities	J Glob Health. 2015;5:020304
Rudan I, Sidhu S, Papana A, Meng SJ, Xin–Wei Y, Wang W, Campbell–Page RM, Demaio AR, Nair H, Sridhar D, Theodoratou E, Dowman B, Adeloye D, Majeed A, Car J, Campbell H, Wang W, Chan KY	Prevalence of rheumatoid arthritis in low and middle income countries: A systematic review and analysis	J Glob Health. 2015;5:010409
Chan KY, Yu XW, Lu JP, Demaio AR, Bowman K, Theodoratou E	Causes of accidental childhood deaths in China in 2010: A systematic review and analysis	J Glob Health. 2015;5:010409
Ting Shi, McLean K, Campbell H, Nair H	The etiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta–analysis	J Glob Health. 2015;5:020408
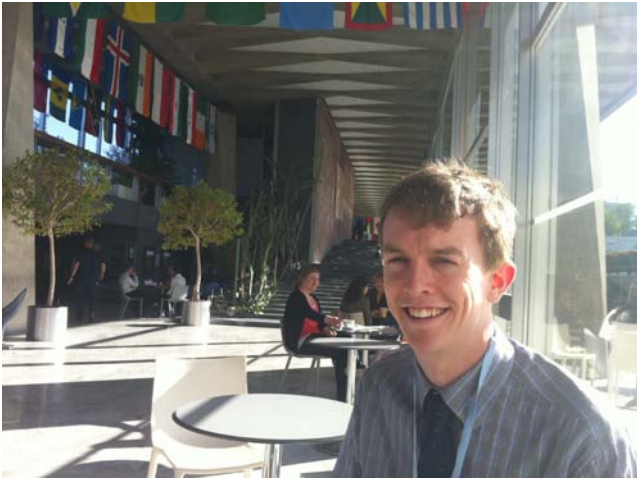
Photo: EUGHS member Donald Waters visited the World Health Organization to present the results of his research on the etiology of newborn infections.

Photo: EUGHS member Donald Waters in the library of the World Health Organization.

Photo: EUGHS member Katy Wong spent several months at the World Health Organization in Geneva as an intern.

EUGHS STUDENT PRESENTATIONS AT INTERNATIONAL MEETINGS

EUGHS students had several successful presentations of their research (**Table 2**) and internships at the WHO (**Box 1**).

Box 1. Internships at the World Health Organization for EUGHS students

- Rachel Burge [2014] – 6 weeks (WHO Headquarters, Geneva, Switzerland)
- Katy Wong [2014] – 5 months (WHO Headquarters, Geneva, Switzerland)
- Mia Cokljat [2015] – 6 weeks (WHO Headquarters, Geneva, Switzerland)
- Kirstie–Ann McPherson [2015] – 6 weeks (WHO Headquarters, Geneva, Switzerland)
- James Gao [2015] – 6 weeks (WHO Headquarters, Geneva, Switzerland)
- Kenneth McLean [2015] – 6 weeks (WHO Headquarters, Geneva, Switzerland)

Table 2. EUGHS student presentations at meetings

STUDENT	MEETING/TOPIC
Andrew McCallum	Meeting with staff of the Department for Child and Adolescent Health and Development, World Health Organization, Geneva, Switzerland, May 2006 (student presentation on role of medical schools in assembling evidence and their role in the International Child Health Review Collaboration)
Amy Agahi, Victoria Anderson, Issrah Jawad Rachel Falconer	Meeting of the World Health Organization's Child Health Epidemiology Reference Group (CHERG): Dubrovnik, Croatia, September 2008 (student presentations of systematic reviews of global burden of disease for a variety of childhood infections)
Rachel Falconer, Issrah Jawad, Sarah Ali, Sameeka Kariyawasam, Sue Johnson, Andy Davis, Felicity Woodward, Joy Ferguson, Jasjot Singhota, Neil Gray	Meeting of the World Health Organization's Child Health Epidemiology Reference Group (CHERG): Dubrovnik, Croatia, September 2009 (student presentations of systematic reviews of global burden of disease for a variety of childhood infections and reviews of effectiveness of interventions against these conditions)
Debajeet Choudhuri, Arnoupe Jhass, Vas Verma, Joy Ferguson, Daisy Higginson, Ang Choon Seong, Alasdair Catto, Julia Webster	Meeting of the Bill and Melinda Gates Foundation's Advisory group on research priorities for emerging interventions against childhood pneumonia, meningitis and influenza: Dubrovnik, Croatia, September 2009 (student presentations of systematic reviews of emerging interventions against childhood pneumonia, meningitis and influenza)
Anna Breakey	Meeting of the World Health Organization's Child Health Epidemiology Reference Group (CHERG): Tarrytown, New York, USA, October 2009 (student presentation of systematic reviews of global burden of disease for childhood infections)
Peter Hanlon	Meeting of the World Health Organization's Child Health Epidemiology Reference Group (CHERG) on the global burden of severe pneumonia in young children: Edinburgh, UK, September 2010 (student presentation of systematic review on severe pneumonia to open meeting)
Alasdair Campbell	World Health Organization's meeting to review recommendations on newborn health, childhood diarrhoea and pneumonia: Geneva, Switzerland, February 2011 (international expert group meeting to undertake GRADE assessment of WHO recommendations for pocketbook of hospital care for children – student presentation on role of medical schools in assembling evidence)
Prasad Palani Velu, Tom K. Roberts	International conference on neonatal sepsis: New Dehli, India, March 2011 (student presentation of systematic reviews of global burden of disease for maternal bacterial, viral and parasitic infections and newborn infections)
Donald Waters	World Health Organization's meeting on equitable investment in child health interventions and EQUIST tool: Geneva, Switzerland, April 2011 (student presentation of application of EQUIST tool on childhood pneumonia in 5 countries)
Donald Waters	UNICEF's meeting on equitable investment in child health interventions and EQUIST tool: Innocenti Centre, Florence, Italy, October 2012 (student presentation of application of EQUIST tool on childhood pneumonia in 5 countries)
Donald Waters, Thomas Williams, Kenneth McLean	Meeting of the World Health Organization's Child Health Epidemiology Reference Group (CHERG) / Maternal and Childhood Epidemiology Estimates (MCEE) on the global child mortality causes: Dubrovnik, Croatia, July 2014 (student presentation of systematic reviews of global burden of disease for maternal and childhood infections)
Anna Badenhorst	Meeting of the Child Health and Nutrition Research Initiative (CHNRI) and Global Coalition of Child Health Centres (GCCHC) on research priorities for global child health: Toronto, Canada, October 2014 (student presentation of global, regional and national capacity to conduct global health research between 1995 and 2010)

MY PERSONAL EXPERIENCE AS WHO INTERN – BY RACHEL BURGE

In the summer of 2014, I was delighted to have the opportunity to undertake an internship at the World Health Organisation Headquarters in Geneva, Switzerland, in the Department of Maternal, Child and Adolescent Health. I was a medical student having just finished my third year of study at Edinburgh University, graduating with an intercalated degree in Infectious Disease and before returning to the third year medical curriculum. Up until that time, I had taken advantage of the many opportunities offered within the university to build my knowledge and understanding of global public health, developing an interest in world current affairs and learning how I may be able to focus my medical career in a globally–minded direction.

I had been involved with the University of Edinburgh Global Health Society since commencing university, and it was through the society and the university staff involved that the internship was organised – for which I will always be so grateful! For me, the opportunity of an internship at the World Health Organisation, an organisation so central to so many current and historical medical global affairs which were so prominent in discussion was an opportunity too good to surpass. Indeed, even despite the big ex-

Photo: EUGHS member Rachel Burge (right) with her host at the World Health Organization, Dr Sachiyo Yoshida (left).

pectations of a passionate young medical student, my time in Geneva still exceeded expectations. The opportunities to meet the people who worked with and in collaboration with the organisation, to ask questions and hear differing views and advice, to get to know how they journeyed into the world of public health, and to get a glimpse into the workings of this huge organisation was invaluable to me. Being able to contribute to this work, although in a small way, was of course an extremely exciting prospect.

For my six week internship, I was given set tasks by my supervisor, Sachiyo Yoshida, a technical officer in the department. Reflecting her own work, my tasks focused more specifically on neonatal and child health. A large portion of my workload focused on the Child Health Nutrition and Research Initiative, which published a methodology in 2009 which aimed to rank research priorities in order to guide research scientists and their funders. In this sense, my work was the beginning of a retrospective study looking at the research which targeted the top 5 research priorities as ranked by the initiative, concerned with reducing the top 5 causes of child mortality. I searched the literature for research published since 2011 up until 2014. Of the relevant studies identified, I then went on to identify their funders, information which could ultimately be used to evaluate the impact of the CHNRI publication.

Aside from this main study, I was able to contribute to the write–up of a Study Protocol, and to the preparations for World Breastfeeding Week – promoting conference within

the headquarters, attending conferences and taking notes for the panel. I enjoyed meeting a speaking with globally–minded people, who had devoted their career to global health, and often had fantastic stories to be told. Aside from my work at WHO, I also met interns working elsewhere in the HQ, and elsewhere in Geneva for other United Nations agencies, spending time getting to know the beautiful city in the summer months with like–minded young aspiring global health geeks.

Once the weeks had so quickly passed and my internship came to an end, I left inspired by both the people I met and the work I had done during my stay in Geneva. I must give special thanks to the University's Global Health Society and the staff involved for arranging the internship, and to the Innovative Initiative Grant at the University of Edinburgh for providing funding, without which I would not have been able to take this opportunity. I have every intention to continue the development of my involvement with glob-

Photo: EUGHS member Rachel Burge (second from the left) with other interns at the World Health Organization in Geneva.

al health and to build upon the foundations for a medical career focused in the direction of global health, and I am sure that my experience at the WHO will influence my interests and choices throughout my future career.

MY PERSONAL EXPERIENCE AS WHO INTERN – BY KATY NUEN–WING WONG

Upon graduating from the master of public health programme at the University of Edinburgh, I aspired to have a practical experience in public health to consolidate what I had learned throughout the course. Doing an internship at the World Health Organization (WHO) was undeniably

a great opportunity to learn the global progress on the enhancement of population health. Therefore, I submitted my application to the WHO website, indicating my great interest in certain projects. Thankfully, I heard from the WHO after a few months of application, and was successfully offered an internship opportunity after a phone interview. Having the background as a registered Chinese medicine practitioner in Hong Kong, I was assigned to the Team of Traditional and Complementary Medicine at the WHO headquarters in Geneva. There, I spent an unforgettable experience of five months.

WHO is the United Nation's leading authority on international public health. Working closely with public health experts around the world and tackling different important health issues was a very challenging and exciting task. It also gave me great motivation to go to work knowing that it would exert great influence to many populations which could directly enhance their health. My main task in the internship was to work with traditional medicine experts on data verification and analysis on the WHO global surveys. Thanks to the epidemiology and statistics training that I received at the University of Edinburgh, I was well–prepared to manage and analyze the survey data obtained from the 193 member states of the WHO. During my internship I was also involved in working on the unprecedented development of the International Classification of Traditional Medicine which would be included in the coming ICD–11. This achievement will make significant contribution to the standardization of the clinical language used by traditional medicine to facilitate information exchange and the integration of complementary medicine into the health care system. All the work I conducted there was evaluated by my supervisors at WHO, whom eventually offered me an exceptional extension of the 3–month internship contract on top of the first contract.

On the other hand, as an intern I got to participate in many training sessions and discussion seminars which helped expand and develop my public health knowledge. I had attended seminars on mental health, palliative care and neglected tropical disease. I also had the privilege of being present at the World Peace Talk of the United Nations to learn the issues regarding world peace and human right. Coincidently, it was the Ebola outbreak period during the internship, hence, I experienced firsthand the outbreak response, leadership, roadmap development, division of labour, press conferences, and even the sharing from experts who were deployed in the field in West Africa. Attending the Ebola meeting with the Director–General of the WHO, Dr Margaret Chan, and the Secretary–General of the United Nations, Dr Ban Ki–moon, on the discussion of Ebola vaccine and treatment was very impressive. I also joined the communication team to contact Ebola experts worldwide to investigate the possible treatments for Ebola.

Another memorable experience was the duty travel to Macao SAR, China, for a WHO training workshop. Working as WHO secretariat, I learned the administration and logistics in organizing an international event. In the training workshop, I got the opportunity to meet with a lot of government officials from the ministries of health of different countries. I had gained great insight from the country leaders on policy–making and international cooperation in consumer protection. Together we had built beautiful memories and friendships.

Apart from the tasks that I performed, I met so many amazing and interesting people from all over the world. I enjoyed very much the working environment at the WHO headquarters in which I worked closely with colleagues with multi–cultural and multi–disciplined backgrounds, which can lead to many brilliant ideas. I had also joined the WHO intern board as a interns coordinator, where I made friends with many amazing interns who will possibly become the public health leaders in the future. During our coffee time and excursions, we discussed a lot on the infec-

Photo: EUGHS member Katy Wong (right) with the Director–General of the World Health Organization, Dr Margaret Chan (left).

tious disease control measures, the development of medicines and the research methodology. It was indeed an excellent platform for young people who share the same aspiration to meet and work towards our goals.

Above all, this internship has exposed me to different global health issues, and allowed me to view traditional medicine from an international perspective. Now I understand a lot more the pathway to develop traditional medicine, in terms of quality and safety, pharmacovigilance capacity, national policies and regulations. It has greatly broadened my horizon to understand health issues in a global context. This internship is a once–in–a–lifetime experience for me. It is definitely something that I would highly recommend for everyone who is interested in public health to apply for.

Photo: EUGHS member Katy Wong (in the middle) with the Team of Traditional/Complementary Medicine at the World Health Organization in Geneva.

Is the right to health compatible with sustainability?

Daniel D Reidpath[1], Sofia Gruskin[2], Pascale Allotey[1]

[1] Global Public Health, School of Medicine and Health Science, Monash University, Selangor, Malaysia

[2] Program on Global Health and Human Rights, Institute for Global Health, University of Southern California, Los Angeles, CA, USA

One of the fundamental human rights is the right of every individual to the enjoyment of the highest attainable standard of health, which we simplify to 'HASH' [1]. The HASH right was first articulated in the preamble to the WHO Constitution (1946) [2]. It appears in Article 12 of the International Covenant on Economic, Social and Cultural Rights (ICESCR) (1966) [3]; and occurs in various human rights treaties (cf [4]).

Fully realizing all human rights immediately and completely is impossible; and that is why the right to HASH is supported by the notion of progressive realisation (cf; ICESCR Article 2(1)[3][3]) [5]. That is, States have an obligation to take steps towards the progressive realisation of the right, with the result that over a period of time HASH, ideally, would be fully realised for each individual in the world [3]. Furthermore, economically developed states have an obligation which extends beyond their borders to progressively support less well developed states in achieving the vision [6].

In the recent manifesto *From public to planetary health,* Horton and colleagues declared their support for the HASH right [7] They went on to declare, *inter alia* that "our patterns of overconsumption are unsustainable and will ultimately cause the collapse of our civilisation", that "the idea of unconstrained progress is a dangerous human illusion", and that "we must conserve, sustain, and make resilient the planetary and human systems on which health depends by giving priority to the well being of all" [7]. There are, however, some fundamental public health challenges and trade–offs that need to be confronted for both HASH and

sustainability agendas to be compatible. The trade–offs arise because, at a population level, the highest attainable standard of health is a standard that is achieved (or progressively realised) through unsustainable levels of consumption.

In 2013 a reasonable benchmark for the average highest attainable standard of health was 83 years of life; ie, the life expectancy in France, Iceland, Italy, Japan, and Switzerland (HASH–83) [8]. An individual's HASH point, (ie, their individual right to the highest attainable standard of health) may actually be higher or lower than the population average; due, for example, to genetic (dis–)advantages. HASH–83, thus, potentially provides a policy benchmark for population performance, but it does not detract from a particular individual's legal right to their (unknowable) true

> There are fundamental public health challenges and trade–offs that need to be confronted for the achievement of the highest attainable standard of health and the sustainability agendas to be compatible. The trade–offs arise because, at a population level, the highest attainable standard of health is a standard that is achieved (or progressively realised) through unsustainable levels of consumption.

HASH. Therefore, and in the absence of specific individual data about adverse social determinants, favourable genes, and adverse pre–existing health states, the best guess for any randomly selected individual from a population (even a population with a life expectancy of 50 years) is that the selected individual has a progressively realisable right to HASH–83.

While we await the progressive realisation of an average HASH–83, we can expect that the current trend in life expectancy will actually increase, as it has been steadily doing over the past century. Here in lies the trade–off between the individual right to HASH and sustainability. The link between resource utilisation and health is well established. Nations with the highest GDP per capita and the highest levels of resource utilisation are the countries with populations achieving the highest standards of health, and populations increasing the HASH point [9].

The *Ecological Footprint* indicator was developed in the late 1990s to create a mechanism for measuring the sustainability of human use of the environment using uniform, globally available data [10]. Country level data allows a comparison of the per capita ecological footprint of each country in the common unit of global hectares of available land per capita (GHa/capita) [11]. Based on this indicator, the estimated sustainable footprint is about 1.8 GHa/capita [12]. The global average GHa/capita is about 2.7; ie, we 'overshoot' the sustainability threshold by 50%. Some countries have a considerably higher GHa/capita than others and currently "... about 84% of the world population lives in countries that run growing ecological deficits" (p.1) [13].

With the latest available ecological footprint data (2008) and life expectancy data from the World Bank for the same year [14], we charted the relationship between the per cap-

> The fundamental individual right to the highest attainable standard of health may need to focus MORE on the quality and not the quantity of life. At best we should claim a fundamental human right to the highest sustainable standard of health – and an obligation to take no more.

ita ecological footprint and average life expectancy in 147 countries (**Figure 1**). The relationship is plotted with a nonlinear quantile regression model at the 5th, 25th, 50th (median), 75th and 95th percentiles. The broken vertical line is the sustainability threshold.

Countries' average life expectancies rapidly increase with an increasing ecological footprint, and plateau (or perhaps decline slightly) after a GHa/capita of about 6. The median regression curve (solid black line), suggest a sustainable average life expectancy of 68 years, The countries with the highest average life expectancies (>80) are all high income countries, with a mean ecological footprint of 5.5 GHa/capita or three times the sustainability threshold.

These data suggest that, on average, the enjoyment of the highest attainable standard of health is most likely to be achieved by those living in the wealthiest countries and relies on the exploitation of the resources of the global commons. Unfortunately, at least some of the ecological footprint of high income countries is in fact transferred back to populations in low income countries in the form of technology [15], suggesting that the sustainable life expectancy may be even lower than 68 years.
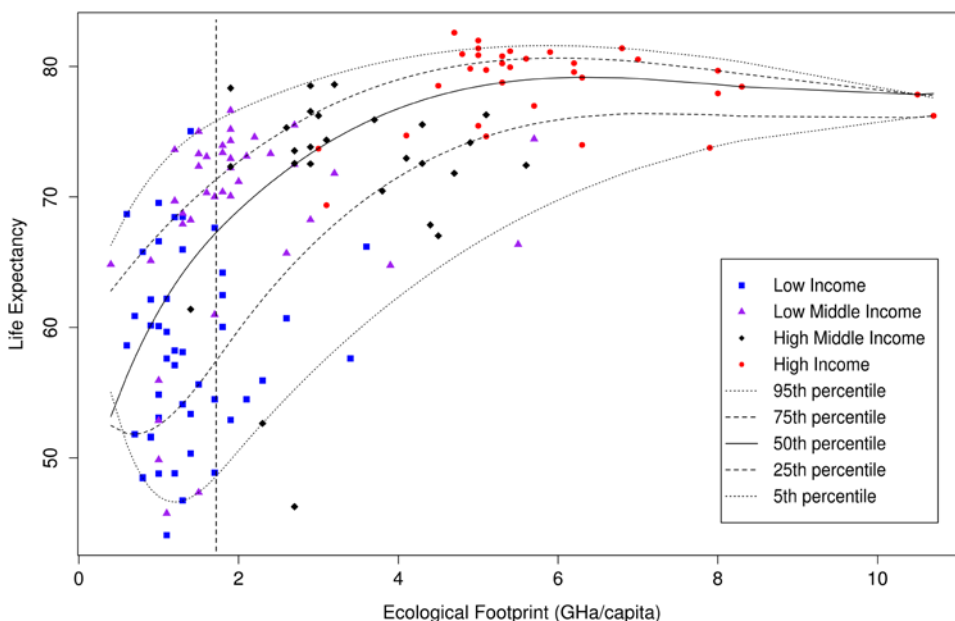
Figure 1. The relationship between the per capita ecological footprint and average life expectancy in 147 countries. GHa/capita – global hectares of available land per capita.

Some countries achieve extremely good standards of health with much lower levels of resource utilisation and much lower levels of national wealth than others. This is shown in **Figure 1** by several of the low–middle income countries. They however still have populations for whom, on average, the HASH–83 has not been realised, and improvements in health will continue to rely on increasing consumption, fuelled by an increasing global population primarily in the poorest and on average least healthy countries.

In 2013 there were 7.2 billion people occupying the world [16]. On current projections the world's population will increase by one third over the next 35 years (2050), giving rise to a total population of 9.6 billion people – and 10.9 billion by 2100 [16]. Each one of these people has a fundamental right to the progressive realisation of the HASH – at least HASH–83.

Let us accept as hyperbole the idea that everyone will achieve their fundamental human right to HASH. Equally, let us accept that the world's population is likely to increase by one third by 2050. With 7 billion people already striving to be better off, we have failed to curtail our destruction of the planet's rainforests [17]. We have failed to preserve the natural fish stocks in our oceans [18,19]. We have seen rates of species extinction in our life time which are associated with major planetary catastrophes [20]. Notwithstanding international commitments to reduce greenhouse gas production, the *rate* of production continues to increase [21,22]. Now add another 2.4 billion people. On very basic measures of sustainability we completely fail.

Those 2.4 billion extra people – the total population of the world a century earlier (1950) – will need food, shelter and health care along with their 7.2 billion companions. They will consume, and if they are like the people of the last quarter of a century, they will aspire to consume more than they do; and they will aspire to greater health than they currently have. We face the tragedy of the commons in which the commons we share is the entire planet. Growth in absolute consumption is not an unreasonable guess and does not auger well for human life on this planet, or for the life of many plant and animal species.

The modern origins of the fundamental human right to the highest attainable standard of health was stirred by an op-

Photo: Courtesy of A. G. Klei, personal collection

timistic vision of human progress and envisioned at a time in which global economic growth was seen as the way to achieve a just world. The reality today is markedly different. A future just world, a fair world, will be achieved not simply by improving the lot of the worst off alone, but simultaneously reducing the position of the best off and actively transferring benefits to the worst off. That is a bitter pill to swallow, made all the harder by the rhetorical assurances of the last quarter of a century that solutions lie in economic growth. Almost without exception, governments around the world are promising their populations that tomorrow (or perhaps the day after that) they will be healthier and wealthier. This is simply untrue. Unless we can reconcile ourselves to a life of (on average) fewer, but hopefully more dignified and rewarding years, and a life of less consumption but greater meaning, then we may lose the opportunity to choose our destiny at all.

The ideas behind *planetary health manifesto* are crucial – a "call to arms" [7]. However without confronting the critical compromises required to realise sustainable public and planetary health, it will remain a manifesto of good intentions. Our fundamental individual right to the highest attainable standard of health may need to focus explicitly on the quality and not necessarily the quantity of that life. At best we can claim a fundamental human right to the highest *sustainable* standard of health – and an obligation to take no more.

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Correspondence to:
Daniel D Reidpath, PhD, HonFRSH
Professor of Population Health & Director SEACO
School of Medicine and Heath Sciences
Monash University
Jalan Lagoon Selatan
Bandar Sunway, 46150, Selangor DE
Malaysiaanya
daniel.reidpath@monash.edu

Career opportunities in global health:
A snapshot of the current employment landscape

Quentin Eichbaum[1], Adam Hoverman[2], William Cherniak[3], Jessica Evert[4], Elahe Nezami[5], Thomas Hall[6]

[1] Vanderbilt University School of Medicine, Nashville, TN, USA

[2] Pacific Northwest University of Health Sciences, Department of Family Medicine, Yakima, WA, USA

[3] University of Toronto, Department of Family and Community Medicine, Toronto, Ontario, Canada and Bridge to Health Medical and Dental, Toronto, Ontario, Canada

[4] Child Family Health International and University of California at San Francisco, San Francisco, CA, USA

[5] Keck School of Medicine, University of Southern California at Los Angeles, CA, USA

[6] University of California at San Francisco, San Francisco, CA, USA

Recent decades have witnessed a burgeoning interest in improving health and health systems in low and middle–income countries (LMIC). With the increase in program funding came parallel increases in the number of university programs in the US and Europe offering concentrations or degrees in a global health field [1–6]. The changes have been brisk and substantial [5–8], and beg the question: What do we know about the global health job market? While a few studies have provided limited insights into the employment landscape, the last comprehensive attempt to answer this question was by Baker 30 years ago [9]. Key questions (as yet largely unanswered) about the current global health job market include:

How satisfactory is the numerical balance between job aspirants and job openings? Are the trend lines of aspirants and openings similar or divergent? Are we at risk of having too many job seekers or too few?

How good is the qualitative match between employer needs and training program outputs? Which competencies are in short supply [10–12]?

What are the contributions, and liabilities, of short–term trainee and volunteer participation in the workforce? How do their contributions fit into the larger picture of the global health workforce [5,10–12]?

Answering these questions will take substantial effort through carefully structured investigations to provide reliable answers. In this article, we present a limited pilot study through a targeted web–based job posting review that does not attempt to answer all these questions but sheds some light on the current landscape of employment opportunities in program management, clinical, and public health–related aspects of global health in international settings.

The investigative team consisted of six physicians, one with a doctorate in psychology, and another with a doctoral degree in Public Health. The team convened in March 2013.

> The demand for global health opportunities over the past decade has fueled a brisk increase in the number of global health training programs, yet the employment opportunities for graduates of such programs remain poorly understood. This pilot survey presents the characteristics of 178 global health employment opportunities available during two specific periods in 2014.

> Understanding the dynamics of the global health job market serves both to guide trainees in their educational choices, and to better inform and improve the structure and content of global health training programs.

Review of online job postings occurred between November 2013 and January 2014. Websites with employment opportunities in global health were identified using the Google search engine. The terms, "Global Health Work," "Global Health Jobs," "Global Health Job Opportunities," "Global Health Workforce," "Global Health Hiring" were searched in August 2013.

These searches returned a large number of results with potential sources of job information. From this sizeable response, for feasibility and efficiency's sake, an initial cohort of 14 websites were selected, limited to English language websites primarily affiliated with organizations in North America, and (if the site permitted access) to a regularly available and rotating list of job postings. A similar consideration in prioritizing this initial pilot list was the Google "PageRank" of each site. Page Rank is an objective measure of a citation's importance that corresponds with users subjective idea of importance [13]. Over the course of the entire survey, 12 further sites were selected to accrue additional postings by applying the same inclusion criteria. The need for additional sites addressed cyclical pauses in available job postings on several sites. Global health workforce employment opportunities were described as positions that

focus on health–related efforts in low– and middle–income countries (LMIC).

The investigative team developed a standardized selection and coding tool using a shared online document matrix. The tool allowed for easy categorization of a number of factors related to the job in question. 26 websites in total were selected for inclusion. Each investigator was assigned one high traffic website with frequent job postings and another with lower traffic and fewer postings. The six investigators then each reviewed a subset of the websites during two 6–week sampling periods. Each investigator retrieved a minimum of 10 job postings during each sampling period. The results were then tabulated and underwent basic statistical analysis.

In this limited, but wide–reaching review of online job postings that included 178 employment opportunities from 26 websites, key findings included:

67% (119/178) of the positions were in non–governmental organizations (NGOs) in both developed countries and LMICs. When combined with multinational organizations such as the World Health Organization (WHO) and the World Bank, the two employer types accounted for 89% (158/178) of the total (**Figure 1**, plate A).

14% (25/178) of the positions involved clinical disciplines primarily medicine. (**Figure 1**, plate B).

50% (89/178) of job posts included the request for applicants to have the kind of knowledge and skills normally acquired in schools of public health offering courses relevant to global health.(**Figure 1**, plate B)

51% (91/178) of the listed opportunities required at least a Master's degree level of qualification or doctoral degree (23%, 41/178) (**Figure 1**, plate C).

84% (149/178) of the positions were program–related. Program–related jobs included planning, program direction, finance, management and other supportive functions (not depicted but subcategorized in **Figure 1**, plate D).

The majority of program–related jobs were identified to be at the senior program management and direction level (58% (87/149) (**Figure 1**, plate D). Second most common were supportive program functions (28% 41/149) followed by other support activities (9% 13/149) and program financing (5% 8/149) (**Figure 1**, plate D). Salary information, which could provide a basis for assessing the strength of de-

Photo: Courtesy of Trisha Pasricha, personal collection
(from the documentary "A Doctor of My Own", directed by T. Pasricha)
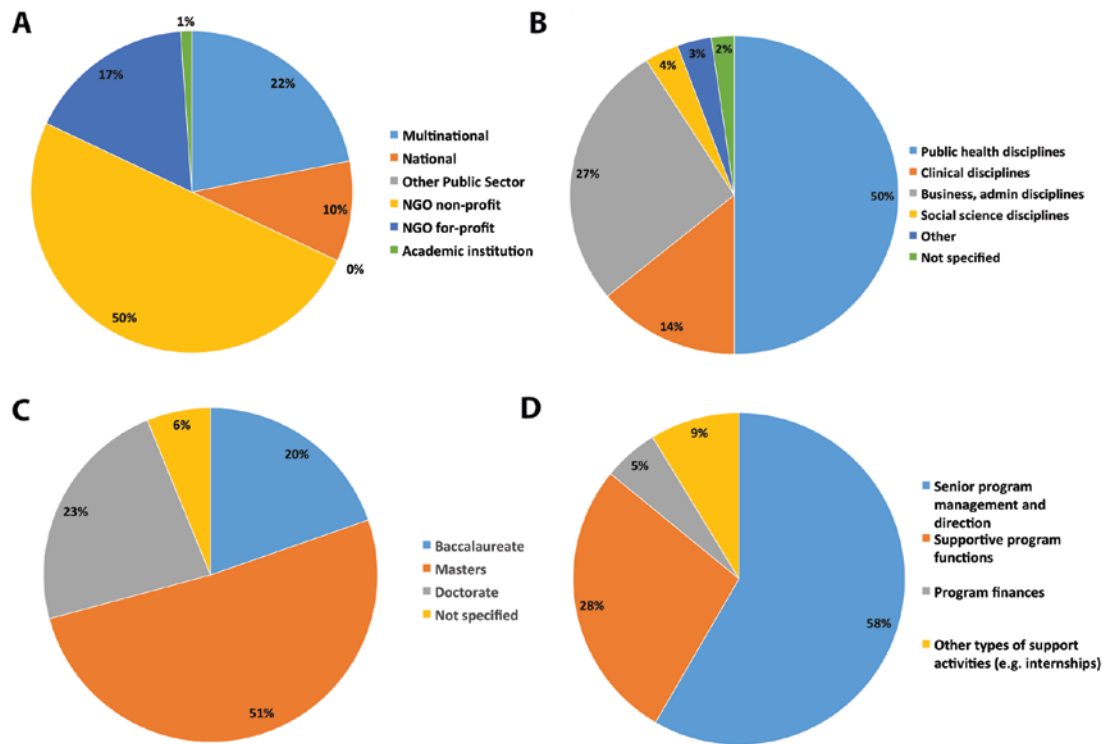
Figure 1. Depiction of survey results of career opportunities in global health. **A)** Breakdown of types of global health employers. **B)** The primary disciplines sought by employers. **C)** Highest academic achievement required or desired by employers. **D)** A sub–categorization of specific function desired in a program–related job.

mand and for calculating a rate of return on a global health job, was provided in only 18% (32/178) of the job offerings. Of those listed, most (56%, 18/32) were in the US$ 61 000 – 90 000 range (**Figure 2**).

The size, characteristics and trends of the global health workforce and jobs available are largely unknown. Our pilot study of internet–based job postings provides a initial snapshot of one view of global health employment opportunities in international settings. Aside from highlighting the many as yet unanswered questions regarding the global health workforce, the study itself has limitations with respect to its specific focus on the job market. These include: small sample size, use of only English language job postings accessible on the internet, the scant salary and benefit information available, and the generally limited scope of positions in LMICs. The salary ranges available may be on the lower end as higher salary jobs may conceivably not be publicized. We did not attempt detailed analysis of the many discrete skills sought by employers, nor did we make follow up phone calls to employers to learn whether they readily filled the advertised positions and with the requisite qualifications.

Despite these limitations our findings have implications for the curricula of global health educational programs and to graduates seeking employment and career opportunities. For instance, our investigation draws attention to the importance of public health training and to program management skills. Global health programs should seek to include training in public health with an emphasis on leadership, planning, management, financial, communication, evaluation and related programmatic skills. Given that 74% of the jobs we surveyed required a Master's degree or higher, the importance of advanced academic credentials is evident. This high level academic qualification has clear im-
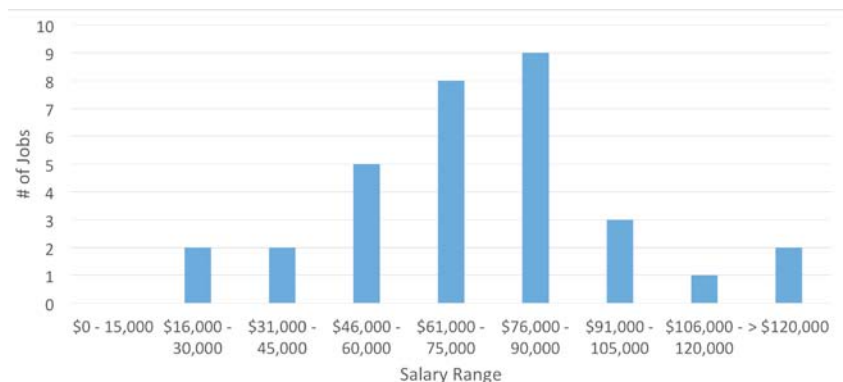
Figure 2. Distribution of global health jobs based on salary range.

plications for students and trainees seeking a career in global health as they will be required to spend more time and tuition in academia before entering the job market. Given the ongoing increases in tuition costs for many undergraduate and advanced degrees, the average salaries offered may appear inadequate for those needing to repay student loans.

Our study suggests the importance of probing more deeply into the dynamics of the global health workforce, including how this workforce is trained and educated as well as the employment opportunities available following the completion of training. Pending an updated investigation along the lines of the Baker 1982 study, several interim studies

might be considered: (1) studies to gain a better understanding of the content and the characteristics of global health (and related) training programs; (2) studies to understand the match between employer needs and applicant qualifications; (3) analyses of the likely trends and stability of the global health job market; (4) surveys of the Global South host countries to determine if training among visitors from the Global North adequately meets their needs; (5) analyses of the intersections between domestic and international employment opportunities, training and career paths. We welcome exchanging views with others interested in learning more about the global health workforce.

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Correspondence to:
Dr Quentin Eichbaum
Vanderbilt University School of Medicine
Vanderbilt University Medical Center TVC 4511C
1301 Medical Center Drive
Nashville, TN 37232–5310, USA
quentin.eichbaum@vanderbilt.edu

Ebola and the need for restructuring pharmaceutical incentives

Abraar Karan[1], Thomas Pogge[2]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[2]Yale University, Department of Philosophy, New Haven, CT, USA

The Ebola outbreak in West Africa has claimed the lives of over 9000 people largely due to a combination of poor health care infrastructure in affected countries, traditional beliefs and cultural practices, including the consumption of bushmeat and certain burial rituals that have amplified transmission, and the lack of therapeutic interventions such as medications and vaccinations [1,2]. Ebola virus was discovered in 1976, and since then there have been over 30 outbreaks, the majority occurring in Sub-Saharan Africa, yet development of medications has been negligible [3]. Moreover, while the current epidemic has spurred a new race to develop Ebola vaccines and treatment regimens, the current patent system makes it unlikely that people in the most afflicted nations will have access to such vaccines or medications when they are brought to market without the assistance of development aid initiatives from the United Nations (UN), World Health Organization, the GAVI Alliance and other multinational global entities.

While there have been just a handful of deaths outside of Africa, the vast majority of fatalities from Ebola virus have been in low-income African countries. This is largely because wealthy nations have been able to mount strong public health responses through providing effective medical care to stabilize patients, enforcing strict isolation protocols to prevent further transmission, and accessing experimental therapies for use in their populations, including ZMapp and TKM-Ebola [4]. Several other drugs and vaccines are also under rapid development, most notably ChAd3, which was recently highlighted in the *New England Journal of Medicine* as having immunogenicity in humans [5]. According to a February 2015 press release from the UN and WHO, large-scale research trials have now begun in Liberia, with Sierra Leone and Guinea to follow soon [6]. But when these drugs are fully approved for international distribution, will they be affordable for all? Given the current global drug-patenting paradigm with its 20-year delay on generic competition, patent holders can set drug prices as high as they please, effectively making their drugs inaccessible to poor populations.

Moreover, with a limited supply of Ebola medications even in the near future, wealthy nations will likely stockpile the drugs and vaccines as was done with Tamiflu in 2009, preventing poorer nations from accessing therapy to treat those who are currently infected [7]. There is no financial or political mechanism to ensure that drugs and vaccines are

> The West African Ebola epidemic has created market demand for the rapid development of vaccines and therapeutics, but the current global patent system does not ensure that the poor will have access to these products.

available and affordable for the people of Guinea, Liberia, Sierra Leone and other poor nations at high risk of Ebola epidemics. As of December 2014, the GAVI Alliance has made a commitment of US$ 300 million to purchase Ebola vaccines for those in affected countries, but this is only an *ad hoc* solution as opposed to a fundamental restructuring of the system [8].

The affordable provision of treatment for people in West Africa is not only an ethical imperative, but also the best strategy to keep Ebola from spreading to other continents on a larger scale. Ultimately, the international community must intervene to ensure that future Ebola medications are sold at a tiered price to developing countries that are most heavily afflicted. But it remains unclear if this can or will happen.

While making Ebola medications accessible to all will be the challenge going forward, we should also ask why no therapy for this high-fatality virus was brought to market since its discovery 40 years ago. The reason lies in the way our pharmaceutical innovation system is structured. Four years ago, scientists at the National Institute of Allergy and Infectious Disease developed an Ebola vaccine that was able to prevent animal transmission, but no pharmaceutical company was interested in taking it to trial in human subjects [9]. While there are programmes, such as the USAID Emerging Pandemic Threats programme, to detect potential pandemic illness, there is little financial promise for major pharmaceutical companies to invest in vaccines or drugs for these potential threats until they are a threat to countries that have consumers who can afford them [10].

> Despite various *ad hoc* incentives, investment in new medicines for the diseases of the poor has been inadequate; the Health Impact Fund would reliably make these investments lucrative and thus help prevent large outbreaks of such diseases.

Had there been significant Ebola outbreaks in affluent nations rather than in Sub-Saharan Africa in the past few decades, we would likely have an arsenal of medications in stock today. While pharmaceutical companies continue to profit from sales of non-essential medicines, and neglect investments in medicines that are needed mainly by the poor, the global community ends up paying as result. Current estimates by the World Bank put the cost of the Ebola outbreak at upwards of US$ 32.6 billion by the end of 2015 – vastly more than what it would have cost to develop effective therapies to stop the epidemic in its tracks [11].

Ultimately, the approach to controlling developing pandemic diseases is multifold. Strengthening health systems, as discussed by Boozary et al., will be important for controlling the spread of disease [12]. However, without access to medications, strong health systems can only do so much to prevent transmission and provide effective care. To cure patients and suppress further transmission, an effective complement to the current pharmaceutical drug development system is urgently needed (**Table 1**).

Table 1. Mechanisms to incentivize drug development for Ebola and other diseases of the poor

Mechanism	Pros	Cons	Applied to Ebola
United States Orphan Drug Act of 1983	• Provides up to 50% R&D tax credit for research into "orphan disease"* therapies • Provides 7 year patent exclusivity from time of FDA approval • Fast track approval of drugs to avoid delays	• Does not control pricing, meaning drugs may remain prohibitively costly • Does not incentivize drug development for illnesses affecting people outside the USA	• While pharmaceutical companies are incentivized to produce Ebola medications under this act, they are in no way required to provide these at a reasonable cost to those in West Africa or elsewhere
Priority Review Vouchers	• Allows up to one year advancement in patent approval for blockbuster drug when separate patent is concurrently filed for neglected tropical disease† therapy • No increase in cost to tax payers • Vouchers can be sold to other companies for cash or royalties	• Does not control pricing, meaning drugs may remain prohibitively costly • Low use as of 2014 – only 4 vouchers since the program's inception in 2007	• While pharmaceutical companies are incentivized to produce Ebola medications under this system, they are in no way required to provide these at a reasonable cost to those in West Africa or elsewhere
Advanced Market Commitments (AMC)	• Governments and other agencies provide subsidies for a fixed number of vaccines sold at lower cost in low-income regions	• Limited funding pool that must be reassessed for each development with no guaranteed source of renewal • No incentive to ensure vaccines reach those in need	• If various international entities and the USA government can supply sufficient funding, an AMC could help produce vaccines for global distribution. However, governments alone would be responsible to deliver vaccines to those in need.
Compulsory Licensing	• Ensures that existing patented drugs are available at an affordable price by allowing domestic generic manufacturing before patent period expires	• Does not incentivize drug companies to research and develop medications for illnesses that affect the poor, even if they cause great morbidity and mortality	• Because Ebola has threatened those in the USA and other wealthy nations, medications are now in mass development. If companies keep drug prices prohibitively high, governments can technically issue compulsory licenses to overcome this.
Health Impact Fund	• Focuses R&D on illnesses causing the most morbidity and mortality • Ensures affordable drugs as sales must occur at cost of production • Creates incentive for companies to facilitate drug delivery and ensure positive health outcomes • Allows for competition in an untapped market while not affecting the current patent system	• Wealthy countries would contribute up to 0.03% of their GNI	• Pharmaceutical companies would be incentivized to produce medicines whether Ebola crossed borders or not because of the potential global health impact at stake. They would also be incentivized to aid governments in ensuring that medications reached those in need to improve health outcomes.

R&D – Research & Development, FDA – Food and Drug Administration, AMC – Advance Market Commitment, GNI – Gross National Income
*Orphan diseases are those classified as affecting fewer than 200 000 people in the USA.
†A full list of neglected tropical diseases by the World Health Organization: http://www.who.int/neglected_diseases/diseases/en/.

As described in detail in *The Lancet* by Banerjee et al., the Health Impact Fund (HIF) can play this role and help overcome the current inefficiencies and inequities of the patent system [13]. The HIF would give pharmaceutical innovators the option of registering any new medicine, thereby agreeing to provide it at cost anywhere it is needed. In exchange, the firm is rewarded based on the drug's actual health impact, in essence its success in reducing morbidity and mortality. The HIF would pay out a fixed amount of money each year, divided among the registered medicines according to their respective health impact. The HIF would be most attractive for products that are expected to have a large global health impact but relatively low profitability under conventional monopoly pricing. If most countries

agreed to contribute around 0.01% of their GNI, the HIF could get started with annual reward pools of US$ 6 billion.

Ebola is no isolated case. Several hundred new infectious diseases have emerged in the last century, mostly in low-income regions, and under present rules global market forces have proven insufficient to promote innovation. By rewarding health impact regardless of the patient's socio-economic status, the HIF would provide strong incentives to study such diseases, to develop remedies against them and to promote optimal use of treatments even in the poorest regions [14]. The HIF would answer a moral imperative—to respect and protect the health and lives of the poor—as well as a prudential one—to be smart and proactive in our perennial battle against disease.

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Correspondence to:
Abraar Karan
1218 S Barrington Ave.
Los Angeles, CA 90024
abraar.karan@gmail.com

A neglected priority?
The importance of surgery in tackling global health inequalities

Ewan D. Kennedy[1], Cameron J. Fairfield[1], Stuart J. Fergusson[2]

[1] Medical student, The College of Medicine and Veterinary Medicine, The University of Edinburgh, Edinburgh, Scotland, UK
[2] Specialty registrar in General Surgery, Wishaw General Hospital, Wishaw, Scotland, UK

"I was thinking that I was already dead... now I can talk with you people, I'm so happy!" These words, spoken quietly but with great warmth by a young woman devastated by a vesicovaginal fistula and restored to dignity through compassionate operative treatment, cut cleanly through divides of geography, culture, and class. More eloquently than any statistic she speaks of the life–changing and life–saving importance of surgical services in all health care systems. The woman's testimony features in Jaymie Ang Henry's film, 'The Right to Heal' [1], a deeply moving piece of advocacy that makes a clear case for focusing far greater global attention on the huge need to achieve more equitable access to essential surgery. This is the case we take up here, with a particular focus on the needs of sub–Saharan Africa.

GLOBAL SURGICAL NEEDS

Every year an estimated 234 million major operations are performed worldwide, yet only 3.5% of procedures are performed in the poorest third of the world's population [2].

The Disease Control Priorities for Developing Countries Project reported that 11%–15% of the global disease burden is amenable to surgical treatment [3]. This report also estimated the impact of surgical disease through disability–adjusted life years (DALYs) – a metric which combines 'number of years lived with disability' with 'years of life lost' through death prior to anticipated life expectancy. DALYs were considerably higher in low and middle income countries (LMICs), ranging from a high on the African continent of 38 DALYs per 1000 population to a worldwide low in the Americas of 21 per 1000. However, these figures do not account for a huge range of other surgical diseases.

There is a paucity of patient–level data on surgical outcomes in LMICs [4], and it is likely that LMICs are afflicted both by poor access to surgical services and the highest levels of adverse surgical outcomes. Access to essential surgical care, taken for granted in developed health care systems, remains unavailable to many of the world's poorest [2,5].

SURGICAL CARE PROVISION IN SUB–SAHARAN AFRICA

Little definitive knowledge about volume and availability of surgical care in sub–Saharan Africa exists as most evidence is anecdotal. Estimates suggest the burden of unmet need is vast [2]. **Figure 1** shows a representation of world territory size proportional to the global medical workforce located in that area, vividly demonstrating the region's profound shortage of doctors in general.

This shortage is particularly marked with regard to surgeons. **Figure 2** illustrates the low number of surgeons per head of population in select African nations. Surgical specialists are in particularly short supply: Nigeria had 1 paediatric surgeon per 2.2 million children in 2003 [9]. Surgeons are also inequitably distributed throughout sub–Saharan African countries: 80%–90% of surgeons work in urban areas, although
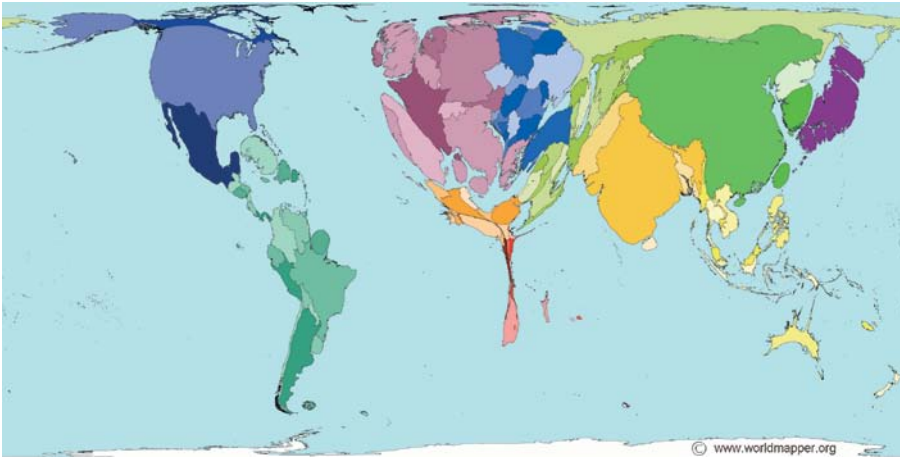
Figure 1. Proportionate distribution of doctors worldwide. Source: Worldmapper.org [6], Creative Commons Licence for this image.

85% of the population live in rural regions [7]. This situation arises from unattractive rural conditions such as poor working environment, lack of transport, limited career progression, lack of exposure to surgical techniques and the migration of other health care workers. Doctor migration, or 'brain drain', is a huge problem in sub–Saharan Africa.
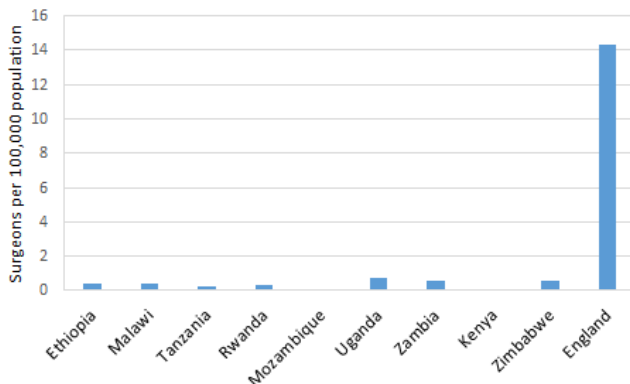
Figure 2. Number of surgeons per capita in selected countries. Source: The Royal College of Surgeons of England and the College of Surgeons of East Central and Southern Africa (COSECSA) [7,8].

Surgery has a neglected profile in global health, taking a back seat to other priorities despite the fact that surgical diseases disproportionately affect the world's poorest people. There is no specific mention of surgery in the Millennium Development Goals despite this disease burden. Surgery will need to assume a more prominent role in public health as the balance is tipped toward an increasing prevalence of surgical conditions.

The lack of human resources, infrastructure and facilities means the need for surgical services is immense. Most district hospital operating theatres in Malawi do not have dedicated staff and half lack adequate instruments, including sutures, for common surgical procedures [10]. In Chad, Madagascar, Niger, Burkina Faso and Ethiopia, Caesarean–sections only account for 0.4–1.0% of all births, while the general consensus for an ideal global Caesarean section rate is 10–15% [5]. This suggests that this life–saving procedure is not available to most expectant women, and must be a key reason why women in sub–Saharan Africa have an adult lifetime maternal mortality risk of 1 in 38, compared with 1 in 3700 in developed countries [11].

SURGERY AND GLOBAL HEALTH PRIORITIES

The global health successes of the last thirty years have been largely against infectious diseases. Public health organisations are approaching eradication of polio and small-pox, and mortality from HIV/AIDS, tuberculosis and malaria are declining due to well–established interventions [12]. Largely through LMICs industrialisation, improved health care systems and the successes of the global drive to eradicate infectious disease, the usual trends of disease have been altered and non–communicable diseases now surpass infectious diseases as leading contributors to morbidity and mortality [13].

Surgery has a neglected profile in global health, taking a back seat to other priorities despite the fact that surgical diseases disproportionately affect the world's poorest people [13]. Arguably, essential surgical care should be part of the basic right to health care. Surgery will need to assume a more prominent role in public health as the balance is tipped toward an increasing prevalence of surgical conditions.

There is no specific mention of surgery in the Millennium Development Goals (MDGs) despite the burden of surgi-

> Recent cost-effectiveness studies refute the attitude that surgery is an unaffordable financial expense in the developing world. They demonstrate that simple and safe surgery at district hospitals represents a cost-effective component of healthcare which not only transforms the life of an individual, but supports community productivity through the prevention of disability.

cally–amenable disease. Additionally there has been little mention of how improving basic surgical care would help to achieve targets within the MDGs especially MDG4 (reduce child mortality), MDG5 (improve maternal health) and MDG6 (combat HIV/AIDS) [14]. Traditionally surgery has been viewed as an expensive tool of last resort after a failure of medical therapy and one that has limited value as a prophylactic intervention.

THE CASE FOR PRIORITISING SURGICAL CARE

The existence of profound gaps in surgical provision within sub–Saharan Africa may not be surprising, but the case for focusing on surgical care development may not be immediately obvious in the context of so much unmet need. We put forward two important arguments.

Cost–effectiveness

Recent cost–effectiveness studies [15] refute the popular attitude that surgery is an unaffordable financial expense in the developing world. They demonstrate that simple and safe surgery at district hospitals represents a cost–effective component of health care which not only transforms the life of an individual; rather it also has the capacity to empower communities to enter work and support the local economy by preventing disability.

Surgical treatment of cataract provides an excellent example of the role that surgery can play in restoration of livelihoods. After living for two years with congenital cataract, the young child pictured in the illustration was granted the gift of clear sight through the charity Orbis following an operation. This enabled him to play with friends and attend school for the first time allowing him to receive an education.

This simple and effective surgery provides a child the possibility of a future free from the disabling condition and also frees another individual who would likely have been involved in their care. The link between surgical intervention in cataract and improved quality of life as well as reduction in poverty in LMICs is demonstrable through large studies. One study [16] showed surgical treatment of cataract leads to sustained improvement in per capita expenditure of the household of the patient for up to 6 years. In the Philippines, per capita expenditure increased from US$ 22 to US$ 39 per person per month in those receiving curative surgery compared to an increase of US$ 29 to US$ 37 in healthy controls.

Photo: Child treated for congenital cataract
(Courtesy of Orbis; http://gbr.orbis.org/news/entry/simul–can–play; used with permission)

Data from Grimes et al [15] demonstrate that the cost–effectiveness of surgical interventions compares well with other public health measures (**Figure 3**) and makes a powerful case that their utility has been unfairly neglected.

Wider health benefits

An improvement in surgical care would have wider benefits on health problems beyond specifically surgical disease. Basic surgical provision provides a valuable adjunct to the medical and social therapies already adopted by proponents of MDGs 4, 5 and 6 [14] as mentioned above.

With regard to MDG6 (combating HIV/AIDS), improving surgical provision would give clear support to this objective. As little as 18% of surgical centres in LMICs provide appropriate eye pro-
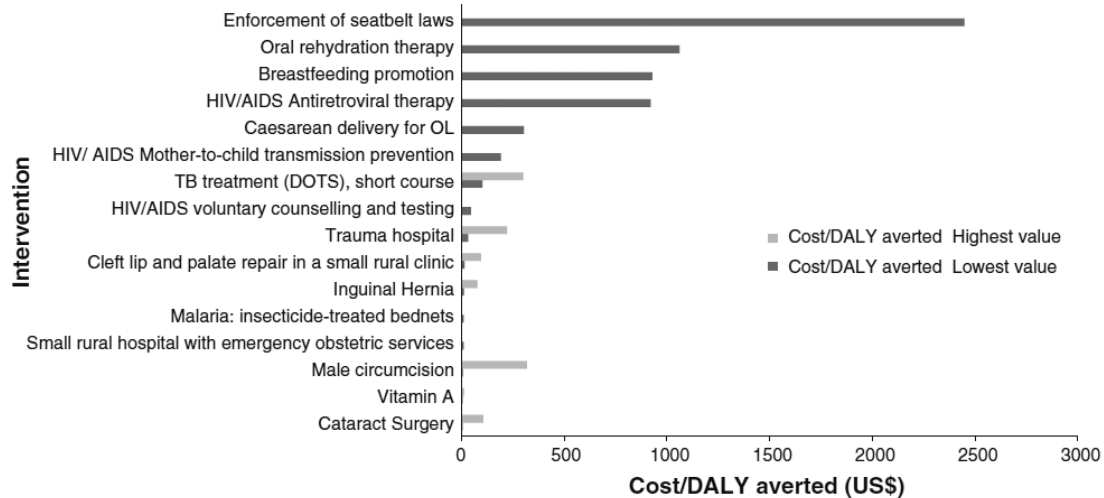
Figure 3. The cost–effectiveness of surgical and non–surgical public health interventions. Source: Grimes et al. [15], used with permission.

tection and 48% provide a sharps bin for surgical staff during surgical procedures [14]. Basic training and provision of protective equipment would likely reduce the rates of HIV transmission. Similarly, despite evidence to support Caesarean sections in HIV–positive mothers, 54 countries have Caesarean section rates under 10% [5]. The majority of these countries are in Africa where HIV rates are extremely high ranging from 1.3–12% per region [12]. Striving to increase the availability of Caesarean sections in these areas will be a useful tool in the control of HIV.

THE WAY AHEAD

The world can no longer afford to neglect the importance of surgical services. How then does the global community tackle the immense global inequalities in surgical care? We offer some evidence–based suggestions.

Personnel

In view of the profound manpower shortages outlined above, a key goal for all LMICs is to increase the size and skill of their surgical workforce, and to distribute that workforce more equitably within countries. Appropriate remuneration and quality specialist training are important to keep doctors engaged. There are many successful training schemes in LMICs which have been established to equip national surgeons to meet local needs [17].

Nevertheless, the acute shortage of medical staff has meant that a central plank in the health care delivery strategy of many LMICs has been the development of a cadre of para-medical professionals, who in some countries undertake the majority of surgical procedures, particularly in smaller

district hospitals, with good results [18]. Their professional development should continue to be supported.

Infrastructure and equipment

Equipment and infrastructure gaps in LMICs are well documented [14] and efforts to improve global surgical provision must include efforts to address this problem. In a recent convenience sample of 70 hospitals across 7 LMICs [19], only 59% of hospitals had a pulse oximeter in every theatre, with 33% having a pulse oximeter in recovery facilities.

Well–meaning but inappropriate donations can be unhelpful, and so gifts of equipment must be carefully planned and evaluated. Thoughtfully planned interventions such as the Lifebox Foundation's supply of purpose–built pulse oximeters to LMIC settings, with associated training, provide an example of the effectiveness of best practice in this area [20].

Academic activity

One of the activities which has undergirded success in other areas of health care development has been focused academic work. Although there are many health research institutions in LMICs, the volume and influence of their activities needs significant further improvement [4]. International partnerships and collaborative work such as the GlobalSurg study of emergency abdominal surgery outcomes [21] can be powerful drivers of a strong local audit culture that needs developed.

In the age of the internet, partners have the opportunity to bring high–quality academic training directly to surgeons working within LMICs which will contribute to the effort to avoid 'brain drain' [22].

Advocacy

Finally, achieving greater focus on surgery as a developmental priority will also require political engagement [23], something that surgeons find difficult given their overwhelming clinical workload. This will mean advancing international collaborations such as the World Health Organization's Global Initiative for Emergency and Essential Surgical Care [24], and reframing some surgical needs in terms of current political priorities, such as the 2015 Millennium Development Goals [14].

With a comprehensive plan of engagement, surgery can be redeemed from its "neglected stepchild"[25] status in global health, with huge benefits to the global population.
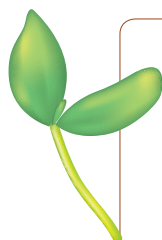
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Correspondence to:
Ewan D. Kennedy
Medical student
The College of Medicine and Veterinary Medicine
The University of Edinburgh
Edinburgh, Scotland, UK
E.D.Kennedy@doctors.org.uk

PAPERS

Impact on inequities in health indicators: Effect of implementing the integrated management of neonatal and childhood illness programme in Haryana, India

Sunita Taneja[1], Shikhar Bahl[1], Sarmila Mazumder[1], Jose Martines[2], Nita Bhandari[1], Maharaj Kishan Bhan[3]

[1] Centre for Health Research and Development, Society for Applied Studies, New Delhi, India
[2] Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Norway
[3] Ministry of Science and Technology, Government of India, New Delhi, India

Background A trial to evaluate the Integrated Management of Neonatal and Childhood Illness (IMNCI) strategy showed that the intervention resulted in lower infant mortality and improved infant care practices. In this paper, we present the results of a secondary analysis to examine the effect of the IMNCI strategy on inequities in health indicators.

Methods The trial was a cluster–randomized controlled trial in 18 primary health centre areas. For this analysis, the population was divided into subgroups by wealth status (using Principal Component Analysis), religion and caste, education of mother and sex of the infant. Multiple linear regression analysis was used to examine inequity gradients in neonatal and post–neonatal mortality, care practices and care seeking, and the differences in these gradients between intervention and control clusters.

Findings Inequity in post–neonatal infant mortality by wealth status was lower in the intervention as compared to control clusters (adjusted difference in gradients 2.2 per 1000, 95% confidence interval (CI) 0 to 4.4 per 1000, $P=0.053$). The intervention had no effect on inequities in neonatal mortality. The intervention resulted in a larger effect on breastfeeding within one hour of birth in poorer families (difference in inequity gradients 3.0%, CI 1.5 to 4.5, $P<0.001$), in lower caste and minorities families, and in infants of mothers with fewer years of schooling. The intervention also reduced gender inequity in care seeking for severe neonatal illness from an appropriate provider (difference in inequity gradients 9.3%, CI 0.4 to 18.2, $P=0.042$).

Conclusions Implementation of IMNCI reduced inequities in post–neonatal mortality, and newborn care practices (particularly starting breastfeeding within an hour of birth) and health care–seeking for severe illness. In spite of the intervention substantial inequities remained in the intervention group and therefore further efforts to ensure that health programs reach the vulnerable population subgroups are required.

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Correspondence to:

Maharaj Kishan Bhan
National Science Professor
Indian Institute of Technology
F-14, Hauz Khas Enclave
New Delhi-110016
India
rajkbhan@gmail.com

In human rights terms, the word equity represents equality and fairness. It is synonymous with the notion of distributive justice, or fair distribution of good things within a society, whether they may be material pos-

sessions, access to health care or simply survival. Health equity has been defined as the absence of systematic disparities in health (or its social determinants) between more and less advantaged groups [1].

Health indicators such as infant mortality have improved in India over time but still continue to be differential across gender, caste, wealth, education and geography [2]. For example, the National Family Health Survey 2005–2006 showed that infant mortality was 70 per 1000 live births for the poorest and 29 per 1000 for the least poor, 42 and 62 per 1000 live births for urban and rural areas respectively, and 70 and 26 per 1000 live births for those with illiterate mothers and mothers with 12 or more years of schooling respectively. In the past few years India's economic growth has been impressive, but neither the distribution of wealth generated by economic growth nor direct investments in health infrastructure and support systems have been equitably distributed. The result is that poorer families are less likely to access maternal and child health services than wealthier ones. In addition to economic inequity in access to health care, there are social inequities as well. For example, girls, infants from lower caste families and those with illiterate mothers are less likely to receive health care than boys, infants from higher caste families and those with mothers who have completed secondary school.

In 2002, implementation of the Integrated Management of Neonatal and Childhood Illness (IMNCI) strategy was started in India. In addition to treatment of common neonatal and childhood illnesses, IMNCI included home visits to all newborns in the first week of life, and community mobilization activities. We conducted a cluster randomized trial to evaluate IMNCI and found that its implementation resulted in 15% lower infant mortality in the intervention clusters. We also found a substantial improvement in the home based newborn care practices such as initiation of breast feeding within an hour, exclusive breast feeding at four weeks, delayed bathing and appropriate cord care, and in treatment seeking practices in the intervention clusters [3].

Most large studies to evaluate the effect of interventions on newborn and child mortality report only overall results, and not the effect in vulnerable population subgroups. We believe that for an intervention shown to be efficacious in a representative population, several factors require attention when translating research findings to program policy; these include intervention impact on vulnerable groups. We therefore hypothesized that IMNCI implementation would result in a reduction of inequity in neonatal and post–neonatal mortality, health care for illness and in newborn care practices. In this paper we present the results of a secondary analysis to examine the extent to which the IMNCI implementation changed the prevailing health inequities.

METHODS

Methods of the main trial

The methods of the cluster–randomized trial evaluating IMNCI have been previously published and are briefly summarized below [3].

Setting

The trial was conducted in 18 rural areas served by primary health centres in district Faridabad, Haryana, India, with a population of 1.1 million. In this setting, about half of the mothers had never been to school; 95% of the women do not work outside home. 25% of the newborns are low birth weight and 60% of sick children sought care from medically unqualified private practitioners [4,5].

Randomization

In order to randomize the primary health centre areas into intervention and control groups, a baseline survey was conducted and information was obtained on proportion of home deliveries, mothers who had never been to school, population per cluster, and neonatal and infant mortality. The clusters were divided into three strata with 6 clusters each according to their baseline neonatal mortality rates. Ten stratified randomization schemes were generated by an independent epidemiologist, of which seven schemes had a similar neonatal mortality rate, proportion of home births, proportion of mothers never been to school and population size in the intervention and control groups. One of these seven schemes was selected by a computer generated random number and was used to allocate the clusters into intervention and control groups.

IMNCI intervention

The intervention was designed following the guidelines defined by the Government of India for IMNCI [6–9]. The study activities in the intervention clusters included:

a) Post–natal home visits during the newborn period: Community health workers in the intervention clusters were trained to conduct home visits; counsel mothers on optimal essential newborn care practices, identify illnesses, treat mild illness and refer newborns with danger signs.

b) Improving health worker skills for case management of neonatal and childhood illness: All staff working in the public health facilities were trained in improving their existing skills for management of sick neonates and children. Training was given using the Government of India IMNCI training module. Formal and informal sector private providers also underwent IMNCI orientation sessions.

c) Strengthening the health system to implement IMNCI: Supervision of community health workers was improved,

workers were provided performance–based incentives, un-interrupted supplies of essential medicines were ensured through village level depots. To improve community awareness of the available services three monthly women's group meetings were conducted in each village.

Routine care

Routine care includes the activities that were provided by the health care system for newborns and children in both intervention and control areas. This care was provided by two types of community health workers (Anganwadi workers and Accredited Social Health Activists or ASHAs), first level health workers (Auxiliary Nurse Midwives) and primary health care physicians. The activities of each category of workers are briefly described below:

Anganwadi workers: Their routine care activities included preschool education, supplementary nutrition and growth monitoring, largely delivered at Anganwadi centres. Their IMNCI–specific activity (only in intervention areas) was to make home visits after birth to promote optimal newborn care practices.

Accredited Social Health Activists (ASHAs): Their routine care activities included promotion of antenatal care, hospital births and immunization and contraception services. Their IMNCI–specific activities (only in intervention areas) were to conduct women's group meetings to promote newborn care and to treat minor illnesses using the IMNCI algorithm.

Auxiliary Nurse Midwives (ANMs): Their routine care activities included provision of immunization, family planning, antenatal care, first level treatment of children with illness and conduction of deliveries. Their IMNCI–specific activity (only in intervention areas) was to treat newborn and childhood illnesses using the IMNCI algorithm.

Primary health care physicians: Their routine care activities included provision of outpatient treatment of childhood illnesses. Their IMNCI–specific activity (only in intervention areas) was to treat newborn and childhood illnesses using the IMNCI algorithm.

Outcome measurement

The primary outcomes of the trial were neonatal and infant mortality, and the secondary outcomes included newborn care practices and care–seeking for illness. The intervention was initiated in January 2007, and data collection for outcome measurement was started in January 2008.

The overall sample size of the study was about 30 000 live births per group, which was calculated for ascertaining a 20% difference in neonatal and infant mortality, the primary outcomes of the study. All live births in the in-tervention and control clusters were visited on day 29 (for ascertaining neonatal mortality) and at 6 and 12 months of age (for ascertaining post–neonatal mortality). Households in the intervention and control areas were allocated to one of the 110 study field workers who were not involved with IMNCI implementation. The workers visited the allocated households every month to identify new pregnancies and inquire about the outcome of previously identified pregnancies. All live births identified by the workers were entered into a database, which was used to generate the due dates to follow up these infants by making home visits. All households with live births were visited on day 29 and at ages 3, 6, 9, and 12 months to document the vital status of the infant by the worker to whom the household was allocated. The worker confirmed the identification of the infant through a set of questions before asking about the health status of the infant. These surveillance workers were not told the intervention status of the clusters. The follow–up procedures were identical in intervention and control clusters. Information was also obtained from all enrolled infants about socio–demographic characteristics and possession of assets at enrolment.

Secondary outcomes, including newborn care practices and treatment seeking for illness, were ascertained in a subset of enrolled infants at day 29 of life. These outcomes were assessed through an interview by a research assistant with the primary caregiver that lasted 45 minutes to an hour. The sample size for these outcomes was 6200 per group, which was calculated to ascertain at least a 10% absolute difference in care seeking from an appropriate provider for neonatal illness. A random sample of enrolled infants in both the intervention and control clusters was selected for ascertaining secondary outcomes in the following manner. All live births identified by the surveillance workers were entered into a database. Dates for their 29–day visit were generated using a computer program. At the same time, one of five enrolled infants was randomly selected by the computer program for an interview for secondary outcomes. The identification numbers of infants selected for interview were communicated to the research assistants of the secondary outcome assessment team a day before the scheduled interview.

Ethical considerations

The study was approved by the ethics review committee of the Society for Applied Studies and World Health Organization. Permissions were also obtained from the state and district authorities. Informed consent was taken from the women with a live birth prior to the first interview. Oversight to the study was provided by a study advisory group and Data Safety Monitoring Board (DSMB).

Secondary analysis for ascertaining impact on equity

Analysis was performed using Stata software version 11 (StataCorp, College Station, TX, USA) and the methods are described below.

Population subgroups

The infants in intervention and control clusters were divided into subgroups based on their families' wealth, religion and caste, mother's years of schooling and the sex of the infant. The wealth of an individual was determined by a wealth index created using primary component analysis based on all of the assets owned by a household. The fact that a household did not own a particular asset that was generally associated with poor households was also used in the calculation of wealth index. The following variables from the initial survey were used to determine the assets owned by a household: the source of drinking water, use of electricity, type of sanitation, type of cooking fuel used, construction materials used for roof, floor and walls of the house, ownership of items like mattress, a pressure cooker, a chair, a cot/bed, a table, an electric fan, a radio/transistor, a black and white television, a colour television, a sewing machine, a mobile telephone, any other telephone, a computer, a refrigerator, a watch or clock, a bicycle, a motorcycle or scooter, an animal–drawn cart, a car, a water pump, a thresher, a tractor, house ownership; number of household members per sleeping room; ownership of a bank or post–office account. An asset score with a mean of 0 and standard deviation of 1 was used in the principal component analysis. Using the score from the wealth index the population was divided into five equal wealth quintiles. Religion and caste was classified into upper caste Hindu, lower caste Hindus (scheduled castes and tribes), and non–Hindu. Maternal education was classified as none, 1–9 years, 10–11 and 12 or more years of schooling.

Inequities in health outcomes

Neonatal mortality, post neonatal mortality, newborn care practices (eg, exclusive breastfeeding within 1 hour) and careseeking from an appropriate provider for danger signs and pneumonia were displayed for intervention and control areas in subgroups by wealth quintiles, religion and caste, maternal education and sex of the infant. We chose to analyze inequities in neonatal and post–neonatal mortality separately because the overall results of IMNCI trial showed that most of the effect of the intervention on infant mortality was attributable to post–neonatal mortality.

In order to visually assess the degree of income–related inequity in the distribution of health outcomes in intervention and control clusters (neonatal deaths, post neonatal deaths, number of infants who initiated breastfeeding with-

in one hour after birth), we used General Lorenz concentration curves. The concentration curve plots the cumulative percentage of the health outcome (y–axis) against the cumulative percentage of the population ranked by wealth quintile, beginning with the poorest, and ending with the richest (x–axis). The curve is expected to be above the diagonal equity line for a negative outcome like mortality indicating that more deaths occur in the poorer than richer quintiles in the population. Conversely, the curve is expected to be below the equity line for a positive outcome such as utilization of health care indicating that relatively lower number of the poorer quintiles has the outcome.

Effect of the intervention on inequity

The results were analyzed through a multiple linear regression model with a health outcome (neonatal mortality, post–neonatal mortality, exclusive breastfeeding within 1 hour and care seeking from an appropriate provider for a danger sign) as the dependent variable and population subgroups (by wealth quintile, religion and caste, level of education of the mother and sex of infant) as the independent variable. This multiple regression model was adjusted for cluster design and possible confounders such as distance of the cluster from the highway and percent of home births in the cluster. Additional covariates were the intervention group (intervention or control) and an interaction term of the intervention with the population subgroup (eg, wealth quintile × intervention group). The regression coefficient of this interaction term, which reflects the difference in inequities between the intervention and control groups, was the main indicator of the effect of the intervention on equity.

RESULTS

Overall results of the IMNCI trial

The overall results of the trial have been published previously [3] but are briefly described here in order to provide the reader an overview of the overall impact of the intervention before presenting the results related to inequities.

A total of 60 702 infants were enrolled into the trial. There were some differences between the intervention and control clusters at baseline. The control clusters had features of urbanization; a higher proportion of houses had private toilets (46% vs 38%) and a lower proportion possessed 'below poverty line' card, the families in the control clusters were nearer to the highway than families in the intervention areas (7.0 km vs 15.3 km) and had lower proportion of home births (65.9% vs 71.9%).

Overall, the infant mortality rate was significantly lower in the intervention clusters than in the control clusters (adjusted hazard ratio 0.85, 95% CI 0.77 to 0.94). The ad-

justed hazard ratio for neonatal mortality rate was 0.91 (0.80 to 1.03) and that for post–neonatal mortality was 0.76 (0.67 to 0.85). The intervention clusters had significant improvement in newborn and infant care practices. For example, almost 41% of the caregivers in the intervention clusters reported starting breastfeeding within an hour of birth, compared with 11.2% in the control clusters (odds ratio 5.21, 95% CI 4.33 to 6.28).

Population sub–groups in intervention and control clusters

The proportion of poorer households and mothers with no formal schooling was slightly lower in the intervention compared with control clusters. Sex was equally distributed across intervention and control clusters. The largest difference between study groups was in the proportion of non–Hindus (8.9% in intervention and 24.3% in control clusters, **Table 1**).

Inequities in health outcomes in the control population

There were large inequities in health outcomes across different population subgroups. Mortality outcomes were substantially higher among more vulnerable population sub–groups. For instance, in the control clusters, post–neonatal mortality was 41.7 per 1000 in the poorest and 14.0 per 1000 live births for the least poor, 36.5 and 18.5 per 1000 live births in non–Hindus and upper caste Hindus, 32.3 and 20.8 per 1000 live births among female and male infants, 36.3 and 9.8 per 1000 live births in infants of mothers with no formal schooling and those with 12 years

or more of schooling. On the other hand, access to health care was lower in the vulnerable population subgroups. In the control clusters, 17.1% and 42.7% of neonates from the poorest and least poor households were taken for health care from an appropriate provider when they had a danger sign. The corresponding values for the same outcome were 12.3% and 38.4% for non–Hindu and upper–caste Hindus, 19.3% and 36.4% of female and male infants, 19.6% and 51.4% of infants of mothers with no formal schooling and 12 or more years of schooling (**Tables 2 to 5**).

Effect of the IMNCI intervention on inequities in health indicators

Inequities in health outcomes in intervention and control clusters are graphically depicted in **Figure 1**. The IMNCI intervention does not appear to substantially change inequities in neonatal mortality but the concentration curves for post–neonatal mortality indicate greater equity in the intervention clusters compared with the control clusters. The intervention clusters also show a more equitable distribution of early initiation of breastfeeding and seeking care for danger signs from an appropriate provider.

The results of multiple linear regression analysis confirmed that IMNCI intervention did not have a significant effect on inequities in neonatal mortality by wealth status, religion and caste, maternal education or gender. The inequities in neonatal mortality were similar in intervention and control groups across different subgroups after adjustment for cluster design and potential confounders (**Table 2**).

The inequities in post–neonatal infant mortality by wealth status were significantly lower in the intervention as compared to control clusters. Post–neonatal mortality was lower by 4.9 per 1000 per wealth quintile when going from the poorest to the least poor in the control group, but only by 2.8 per 1000 per quintile in the intervention group (adjusted difference in gradients 2.2 per 1000, 95% confidence interval 0 to 4.4 per 1000, $P = 0.053$). There were similar differences in gradients across subgroups by religion and caste, gender and years of schooling of the mother but these differences were not statistically significant (**Table 3**).

Among all the outcomes examined in this analysis, inequities in the control group were the smallest for the practice of initiating breastfeeding within 1 hour of birth. The IMNCI intervention substantially increased the prevalence of this practice, and had greater benefit for the more vulnerable population subgroups resulting in inequity gradients that favored infants from poorer families (difference in gradients between intervention and control clusters 3.0%, CI 1.5 to 4.5, $P < 0.001$), lower caste Hindus and non–Hindus (difference in gradients 3.9%, CI 1.8 to 6.0, $P < 0.001$) and mothers with fewer years of schooling (difference in gradients 5.4%, CI 3.4 to 7.4, $P < 0.001$). This pattern of benefi-

Table 1. Population sub–groups in intervention and control clusters

Characteristics of families of recruited infants	Intervention clusters (%)	Control clusters (%)
Wealth quintiles of household:	n = 29 589	n = 30 604
Poorest	5620 (19.0)	6421 (20.9)
Very poor	5380 (18.2)	6660 (21.8)
Poor	5818 (19.7)	6222 (20.3)
Less poor	6039 (20.4)	6001 (19.6)
Least poor	6732 (22.8)	5300 (17.3)
Mother's education level:	n = 29 545	n = 30 499
None	11 220 (38.0)	12 846 (42.1)
1–9 years of schooling	12 238 (41.4)	11 604 (38.1)
10–11 years of schooling	3460 (11.7)	3405 (11.2)
≥12 years of schooling	2627 (8.9)	2644 (8.7)
Sex:	n = 29 667	n = 30 813
Male	15 623 (52.7)	16 252 (52.7)
Female	14 044 (47.3)	14 561 (47.3)
Religion/caste:	n = 29 565	n = 30 577
Upper caste	19 407 (65.6)	16 122 (52.7)
Schedule caste/schedule tribe	7532 (25.5)	7013 (22.9)
Non–Hindu	2626 (8.9)	7442 (24.3)

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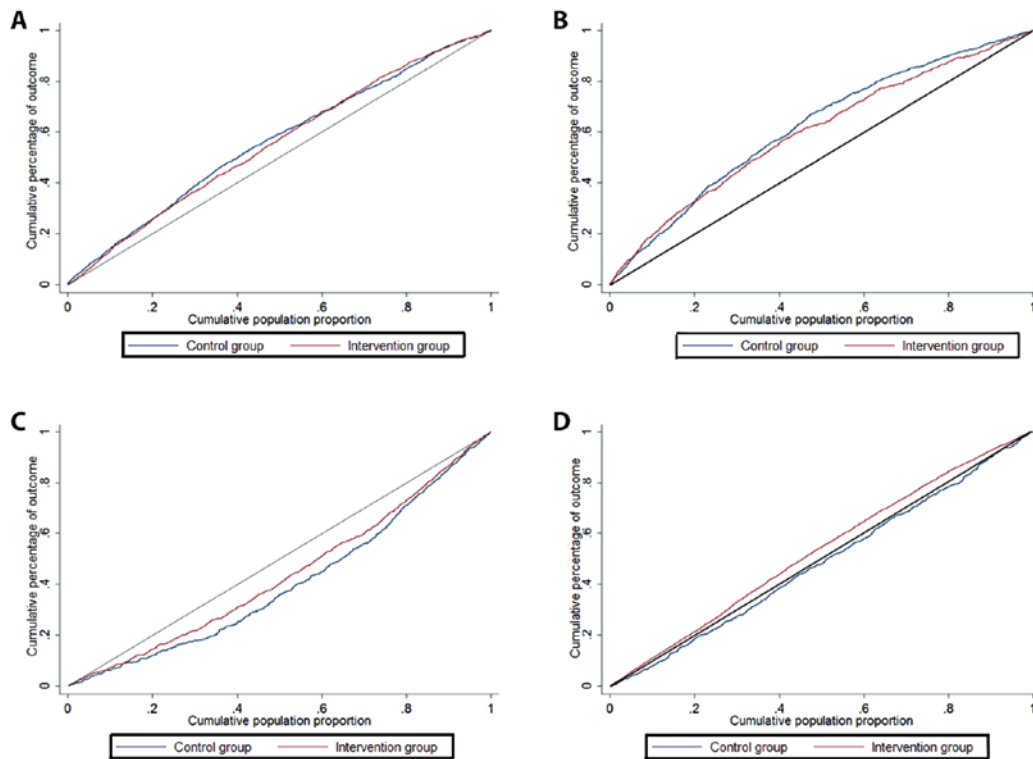
Figure 1. Concentration curves for different health outcomes and wealth quintiles. A. Early initiation of breastfeeding. B. Care seeking for danger signs from an appropriate provider. C. Neonatal mortality D. Post–neonatal mortality.

Table 2. Effect of intervention on inequities in neonatal mortality in the intervention and control clusters

SUBGROUPS (TOTAL INFANTS IN INTERVENTION/CONTROL CLUSTERS)	NO. OF DEATHS (NMR/1000)		DIFFERENCE IN INEQUITY GRADIENT (95% CI)*	P–VALUE
	Intervention (n = 29 667)	Control (n = 30 813)		
Wealth quintile:				
Poorest (5620/6421)	293 (52.1)	348 (54.2)		
Very poor (5380/6660)	248 (46.1)	334 (50.2)		
Poor (5818/6222)	252 (43.3)	224 (36.0)		
Less poor (6039/6001)	241 (39.9)	218 (36.3)		
Least poor (6732/5300)	208 (30.9)	177 (33.4)		
Change in NMR/subgroup (inequity gradient)	−3.6 (−6.0 to −1.2)	−4.1 (−5.9 to −2.3)	0.5 (−2.0 to 2.9)	0.681
Religion and caste:				
Hindu scheduled caste/tribe (7532/7013)	352 (46.7)	330 (47.1)		
Non–Hindu (2626/7442)	117 (44.6)	322 (43.3)		
Hindu Upper Caste (19 407/16 122)	773 (39.8)	648 (40.2)		
Change in NMR/subgroup (inequity gradient)	−0.2 (−3.6 to 3.3)	0.2 (−3.7 to 4.0)	−0.3 (−4.8 to 4.1)	0.872
Gender:				
Female (14 044/14 561)	577 (41.1)	614 (42.2)		
Male (15 623/16 252)	667 (42.7)	712 (43.8)		
Change in NMR/subgroup (inequity gradient)	1.9 (−4.9 to 8.7)	2.0 (−3.1 to 7.2)	−0.1 (−8.7 to 8.4)	0.974
Mother's years of schooling:				
None (11 220/12 846)	537 (47.9)	626 (48.7)		
1–9 years (12 238/11 604)	501 (40.9)	478 (41.2)		
10–11 years (3460/3405)	117 (33.8)	127 (37.3)		
12+ years (2627/2644)	83 (31.6)	57 (21.6)		
Change in NMR/subgroup (inequity gradient)	−2.9 (−5.1 to −0.71)	−4.8 (−8.2 to −1.4)	1.9 (−1.9 to 5.7)	0.296

NMR – neonatal mortality, CI – confidence interval

*Multiple linear regressions adjusted for cluster design and potential confounders (distance of nearest point from PHC to highway, percent of home births, and years of schooling of mother, gender, religion and caste and wealth quintile).

Table 3. Effect of intervention on inequities in post–neonatal mortality in the intervention and control clusters

SUBGROUPS (TOTAL INFANTS IN INTERVENTION/CONTROL CLUSTER)	NO. OF DEATHS (RATE/1000)		DIFFERENCE IN INEQUITY GRADIENTS (95% CI)*	P–VALUE
	Intervention (n = 29 667)	Control (n = 30 813)		
Wealth quintile:				
Poorest (5620/6421)	214 (38.1)	268 (41.7)		
Very poor (5380/6660)	134 (24.9)	219 (32.9)		
Poor (5818/6222)	119 (20.5)	153 (24.6)		
Less poor (6039/6001)	111 (18.4)	91 (15.2)		
Least poor (6732/5300)	100 (14.9)	74 (14.0)		
Change in mortality rate/subgroup (inequity gradient)	–2.8 (–4.2 to –1.3)	–4.9 (–7.0 to –2.8)	2.2 (0 to 4.4)	0.053
Religion and caste:				
Schedule caste and tribe (7532/7013)	229 (30.4)	233 (33.2)		
Non–Hindu (2626/7442)	69 (26.3)	272 (36.5)		
Hindu Upper Caste (19 407/16 122)	379 (19.5)	298 (18.5)		
Change in mortality rate/subgroup (inequity gradient)	–1.8 (–4.1 to 0.51)	–4.8 (–7.7 to –1.8)	3.0 (–0.6 to 6.6)	0.101
Gender:				
Female (14 044/14 561)	392 (27.9)	471 (32.3)		
Male (15 623/16 252)	289 (18.5)	338 (20.8)		
Change in mortality rate/subgroup (inequity gradient)	–9.1 (–12.2 to –6.0)	–10.8 (–14.7 to –6.9)	1.7 (–3.2 to 6.6)	0.479
Mother's years of schooling:				
None (11 220/12 846)	355 (31.6)	466 (36.3)		
1–9 years (12 238/11 604)	247 (20.2)	261 (22.5)		
10–11 years (3460/3405)	52 (15.0)	45 (13.2)		
12+ years (2627/2644)	24 (9.1)	26 (9.8)		
Change in mortality rate/subgroup (inequity gradient)	–4.0 (–6.4 to –1.5)	–5.9 (–8.1 to –3.7)	2.0 (–1.3 to 5.2)	0.222

CI – confidence interval

*Multiple linear regressions adjusted for cluster design and potential confounders (distance of nearest point from PHC to highway, percent of home births, years of schooling of mother, gender, religion and caste and wealth quintile).

cial effects was not seen by infant sex, with boys and girls benefitting equally by the intervention (**Table 4**).

Neonates who were taken for health care when they had a danger sign was inequitably distributed in both control and intervention groups. While the IMNCI intervention improved this outcome overall, the differences in inequity gradients in intervention and control clusters were not statistically significant in subgroups by wealth, religion and caste and maternal education. However, the intervention had an impact on reducing inequity in this outcome by infant's sex. In the control group, only 19.3% of girls compared to 36.3% of severely ill boys were taken for care to an appropriate provider but this difference was reduced in the intervention group with 41.3% of girls and 50.7% of boys taken for appropriate care (difference in gradients 9.3%, CI 0.4 to 18.2, P = 0.042).

DISCUSSION

Main findings

The beneficial effects of the IMNCI intervention on newborn and infant care practices and survival were equitably distributed among population subgroups. The intervention

reduced inequities in post–neonatal mortality between wealth quintiles but did not reduce inequities in neonatal mortality. There was a greater increase in the proportion of neonates who initiated breastfeeding within one hour of birth in the intervention clusters among poorer families, lower caste and minority families and infants of mothers with fewer years of schooling. Care seeking for severe neonatal illness from an appropriate provider improved more for girls reducing gender inequity but inequities in this outcome by wealth, religion and caste and maternal education did not change.

Potential mechanisms that could explain the results

While there was no attempt to specifically target the poorer and other vulnerable populations in the IMNCI strategy, substantial efforts were made to deliver the intervention to the entire population. We believe that this led to the intervention being delivered to a large proportion of vulnerable population subgroups. These vulnerable population subgroups were also more likely to respond positively to counselling advice as evidenced by a greater improvement of appropriate practices like early initiation of breastfeeding among them because it is least demanding in terms of re-

Table 4. Effect of intervention on inequities in breastfeeding initiation within 1 h of birth (as reported by the mother) in intervention and control clusters

Subgroups (total infants in intervention/control clusters)	No. breastfed in first hour (%)		Difference in inequity gradients (95% CI)*	P—value
	Intervention (n = 6204)	Control (n = 6163)		
Wealth quintile:				
Poorest (1201/1231)	527 (43.9)	127 (10.3)		
Very poor (1089/1299)	510 (46.8)	154 (11.9)		
Poor (1182/1278)	517 (43.7)	139 (10.9)		
Less poor (1276/1222)	497 (38.9)	140 (11.5)		
Least poor (1452/1122)	475 (32.7)	128 (11.4)		
Change in % initiated breastfeeding early/subgroup (inequity gradient)	−2.8 (−4.2 to −1.1)	0.4 (−0.3 to 1.0)	−3.0 (−4.5 to −1.5)	<0.001
Religion and caste:				
Schedule caste and tribe (1556/1469)	718 (46.1)	193 (13.1)		
Non–Hindu (526/1420)	238 (45.3)	93 (6.6)		
Hindu Upper Caste (4119/3254)	1569 (38.1)	399 (12.3)		
Change in % initiated breastfeeding early/subgroup (inequity gradient)	−3.4 (−5.2 to −1.7)	−0.5 (−1.2 to 2.1)	−3.9 (−6.0 to −1.8)	<0.001
Gender:				
Female (2893/2845)	1168 (40.4)	323 (11.4)		
Male (3310/3318)	1358 (41.0)	366 (11.0)		
Change in % initiated breastfeeding early/subgroup (inequity gradient)	−0.8 (−2.0 to 3.6)	−0.2 (−2.3 to 1.9)	−1.0 (−2.5 to 4.5)	0.542
Mother's years of schooling:				
None (2465/2687)	1068 (43.3)	237 (8.8)		
1–9 years (2548/2260)	1061 (41.6)	301 (13.3)		
10–11 years (642/637)	253 (39.4)	95 (14.9)		
12+ years (547/574)	144 (26.3)	56 (9.8)		
Change in % initiated breastfeeding early/subgroup (inequity gradient)	−3.1 (−4.9 to −1.3)	2.2 (0.8 to 3.7)	−5.4 (−7.4 to −3.4)	<0.001

CI – confidence interval

*Multiple linear regressions adjusted for cluster design and potential confounders (distance of nearest point from PHC to highway, percent of home births, years of schooling of mother, gender, religion and caste and wealth quintile).

sources on the mother/family. Availability of appropriate health care close to home resulted in improved care seeking for girls perhaps, due to reduced need of financial resources. It has previously been shown in this population that care for girls is not obtained from hospitals and other health facilities because of lower value placed on girls than that on boys and reluctance of families to use meagre financial resources on the health of girls [10].

Impact on the intervention in reducing inequities in post neonatal mortality is evident but was not observed in neonatal mortality. This lack of impact on inequities in neonatal mortality could be because a high proportion of neonatal deaths occur in the first days of life and are related to maternal health care, which was not part of the IMNCI programme. Further, clinical problems in the neonatal period may develop and evolve rapidly to become serious, and require inpatient care, which was also not included in the IMNCI strategy.

There is no statistically significant effect on differences in post–neonatal mortality between boys and girls. However, the mortality rate in boys was lower in intervention group compared to the control group by 2.3 per 1000, whereas the corresponding difference for girls was 4.4 per 1000.

This means that there might be some effect of the improved care seeking in girls on their mortality, but there might other inequities that girls face that limit the effect on the difference in mortality between boys and girls.

Comparison with other studies that have reported impact of interventions on inequities in neonatal and post neonatal mortality

We could only find one study that reported on the impact of IMCI on inequalities in child health [11]. The effect was mixed. Equity differentials for six child health indicators (underweight, stunting, measles immunization, access to treated and untreated bednets, treatment of fever with antimalarials) improved significantly in IMCI districts compared with comparison districts ($P<0.05$), while four indicators (wasting, DPT coverage, caretakers' knowledge of danger signs and appropriate care seeking) improved significantly in comparison districts compared with IMCI districts ($P<0.05$).

A systematic review published in 2014 summarized evidence about the differential effects of interventions on different socio–demographic groups in order to identify interventions that were effective in reducing maternal or

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Table 5. Effect of intervention on inequities in care–seeking from an appropriate provider for a danger sign during the neonatal period in intervention and control clusters

Subgroups (newborns with danger signs in intervention/control groups)	N (%) taken for care to an appropriate provider		Difference in inequity gradients (95% CI)*	P–value
	Intervention (n = 1010)	Control (n = 1269)		
Wealth quintile:				
Poorest (185/257)	60 (32.4)	44 (17.1)		
Very poor (164/258)	58 (35.4)	47 (18.2)		
Poor (187/256)	89 (47.6)	86 (33.6)		
Less poor (208/250)	100 (48.1)	91 (36.4)		
Least poor (264/246)	165 (62.5)	105 (42.7)		
Change in % taken for appropriate care/subgroup (inequity gradient)	4.6 (2.8 to 6.4)	4.0 (2.5 to 5.5)	0.6 (–1.6 to 2.8)	0.554
Religion and caste:				
Schedule caste and tribe (254/304)	97 (38.2)	84 (27.6)		
Non–Hindu (79/308)	18 (22.8)	38 (12.3)		
Hindu Upper Caste (677/653)	359 (53.0)	251 (38.4)		
Change in % taken for appropriate care/subgroup (inequity gradient)	3.9 (–0.2 to 7.9)	2.8 (0.1 to 5.4)	1.1 (–3.9 to 6.1)	0.653
Gender:				
Female (400/514)	165 (41.3)	99 (19.3)		
Male (610/755)	309 (50.7)	275 (36.4)		
Change in % taken for appropriate care/subgroup (inequity gradient)	8.3 (1.6 to 15.1)	17.6 (11.4 to 23.8)	–9.3 (–18.2 to –0.4)	0.042
Mother's years of schooling:				
None (405/555)	156 (38.5)	109 (19.6)		
1–9 years (395/447)	188 (47.6)	144 (32.2)		
10–11 years (119/157)	67 (56.3)	65 (41.4)		
12+ years (91/109)	63 (69.2)	56 (51.4)		
Change in % taken for appropriate care/subgroup (inequity gradient)	5.5 (1.5 to 9.4)	6.5 (2.4 to 10.6)	–1.0 (–6.5 to 4.4)	0.694

CI – confidence interval
*Multiple linear regressions adjusted for cluster design and potential confounders (distance of nearest point from PHC to highway, percent of home births, years of schooling of mother, gender, religion and caste and wealth quintile). Appropriate care provider: Physicians in government and private facilities, auxiliary nurse midwife, Anganwadi worker, or accredited social health activist.

child health inequalities [12]. Eleven of 22 studies included in the review reported on the infant and under–five mortality rate. These studies covered five kinds of interventions: immunization campaigns, nutrition supplement programs, health care provision improvement interventions, demand side interventions, and mixed interventions. The review concluded that the studies on effectiveness of interventions on equity in maternal or child health are limited. The limited evidence showed that the interventions that were effective in reducing inequity included the improvement of health care delivery by outreach methods, using human resources in local areas or provided at the community level nearest to residents and the provision of financial or knowledge support to improve demand side determinants [12]. May be vulnerable groups would benefit more if IMNCI incorporated community based treatment for the less severely ill neonates and leaving referral to health facilities for the severely ill. For neonatal mortality, one of the studies included in the above review reported that participatory women group intervention can substantial reduce socio–economic inequalities in neonatal mortality [13].

Strengths and weaknesses of this analysis

The IMNCI evaluation study was a cluster randomized effectiveness trial with a large sample size involving about 60 000 births and it was therefore possible to study the effect of the intervention on inequities with reasonable precision. Detailed baseline information was available for all births in intervention and control clusters allowing accurate classification into population subgroups by wealth, religion and caste, sex and level of maternal education. There was an independent and similar measurement of outcomes in intervention and control clusters with very low rates of follow up.

There are a couple of weaknesses of this analysis that merit consideration. There are inherent weaknesses of a subgroup analysis, but examination of equity is only possible with such an analysis. There were some baseline differences between intervention and control clusters which could have resulted in some differences in inequity gradients between them. However, we adjusted the analysis for the baseline characteristics that showed important differences between intervention and control clusters. Finally, it is difficult to separate the effects of different components of the IMCI package, or the effect of "IMNCI home visits" that were made to promote newborn care practices from home visits without any health intervention. However, making home visits with no health intervention in the control group was not possible in this pragmatic cluster randomized trial.

Conclusions and implications of this paper

The IMNCI strategy, as implemented in the trial, promotes equity in post–neonatal mortality, newborn care practices, particularly for early initiation of breastfeeding and health care seeking for severe illness for some of the vulnerable population subgroups. However, substantial inequities continue to exist despite the intervention and therefore additional efforts are required for health programs like IMNCI not only to reach vulnerable populations such as mothers and children of families with lower socio–economic status, but also to identify and implement interventions that have a greater effect on reducing inequities.

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Comparing verbal autopsy cause of death findings as determined by physician coding and probabilistic modelling: a public health analysis of 54 000 deaths in Africa and Asia

Peter Byass[1,2,3], Kobus Herbst[4,5], Edward Fottrell[1,6], Mohamed M. Ali[7], Frank Odhiambo[8], Nyaguara Amek[8], Mary J. Hamel[8,9], Kayla F. Laserson[8,10], Kathleen Kahn[1,2], Chodziwadziwa Kabudula[2], Paul Mee[2], Jon Bird[11], Robert Jakob[12], Osman Sankoh[2,5,13], Stephen M. Tollman[1,2,5]

[1] WHO Collaborating Centre for Verbal Autopsy, Umeå Centre for Global Health Research, Umeå University, Sweden

[2] Medical Research Council/Wits University Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[3] IMMPACT, Institute of Applied Health Sciences, School of Medicine and Dentistry, University of Aberdeen, Aberdeen, UK

[4] Africa Centre for Health and Population Studies, University of KwaZulu-Natal, KwaZulu-Natal, South Africa

[5] INDEPTH Network, Accra, Ghana

[6] UCL Institute for Global Health, University College London, London, UK

[7] Eastern Mediterranean Regional Office, World Health Organization, Cairo, Egypt

[8] KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya

[9] CDC Malaria Branch, Atlanta, GA, USA

[10] CDC Center for Global Health, Atlanta, GA, USA

[11] School of Informatics, City University London, London, UK

[12] World Health Organization, Geneva, Switzerland

[13] Hanoi Medical University, Hanoi, Vietnam

Correspondence to:

Prof. Peter Byass
Epidemiology and Global Health
Dept. of Public Health and Clinical Medicine
Umeå University
90187 Umeå
Sweden
peter.byass@umu.se

Background Coverage of civil registration and vital statistics varies globally, with most deaths in Africa and Asia remaining either unregistered or registered without cause of death. One important constraint has been a lack of fit–for–purpose tools for registering deaths and assigning causes in situations where no doctor is involved. Verbal autopsy (interviewing care–givers and witnesses to deaths and interpreting their information into causes of death) is the only available solution. Automated interpretation of verbal autopsy data into cause of death information is essential for rapid, consistent and affordable processing.

Methods Verbal autopsy archives covering 54 182 deaths from five African and Asian countries were sourced on the basis of their geographical, epidemiological and methodological diversity, with existing physician–coded causes of death attributed. These data were unified into the WHO 2012 verbal autopsy standard format, and processed using the InterVA–4 model. Cause–specific mortality fractions from InterVA–4 and physician codes were calculated for each of 60 WHO 2012 cause categories, by age group, sex and source. Results from the two approaches were assessed for concordance and ratios of fractions by cause category. As an alternative metric, the Wilcoxon matched–pairs signed ranks test with two one–sided tests for stochastic equivalence was used.

Findings The overall concordance correlation coefficient between InterVA–4 and physician codes was 0.83 (95% CI 0.75 to 0.91) and this increased to 0.97 (95% CI 0.96 to 0.99) when HIV/AIDS and pulmonary TB deaths were combined into a single category. Over half (53%) of the cause category ratios between InterVA–4 and physician codes by source were not significantly different from unity at the 99% level, increasing to 62% by age group. Wilcoxon tests for stochastic equivalence also demonstrated equivalence.

Conclusions These findings show strong concordance between InterVA–4 and physician–coded findings over this large and diverse data set. Although these analyses cannot prove that either approach constitutes absolute truth, there was high public health equivalence between the findings. Given the urgent need for adequate cause of death data from settings where deaths currently pass unregistered, and since the WHO 2012 verbal autopsy standard and InterVA–4 tools represent relatively simple, cheap and available methods for determining cause of death on a large scale, they should be used as current tools of choice to fill gaps in cause of death data.

"Civil registration and vital statistics don't quicken everyone's pulse." So wrote Richard Horton [1] in summarising the first Global Summit on Civil Registration and Vital Statistics (CRVS), held in Bangkok in April 2013. But, as was clear from that meeting, global understanding of public health depends on having an adequately comprehensive overview of cause–specific mortality patterns at the population level. Counting people and their life events is a big part of what needs to be done more effectively and comprehensively [2]; added to that is the need to attribute cause to deaths in a systematic, rapid, consistent and cost–effective way.

Unsatisfactory progress in CRVS over recent decades lay at the heart of the four major objectives of the WHO Commission on Information and Accountability for Women's and Children's Health (COIA) [3]. Accountability at every level ultimately depends on effectively counting individuals, and then making good use of those data. Implementation of COIA's recommendations was entrusted to an independent Evidence Review Group (iERG), which, in its 2013 report [4], acknowledged that COIA's recommendation on enhancing CRVS will be "difficult or impossible to achieve" by the target date of 2015. Instead, iERG now recommends making effective CRVS a post–2015 development target. While there are evidently many practical obstacles to achieving reliable CRVS on a global scale, one prerequisite component is the availability of fit–for–purpose tools for registering deaths and assigning cause of death. Such tools must be openly accessible, and be capable of delivering consistent and systematic mortality data in a timely and cost–effective manner.

Verbal autopsy (VA; interviewing a care–giver, relative or witness after a death, and using the interview material to determine cause of death) is seen as an essential interim approach for filling in some of the gaps in global knowledge on cause–specific mortality [5], which can otherwise only be estimated [6]. Although, in the long–term, one might hope for universal physician certification of deaths, undertaken methodically and rigorously, this will not be the case for most deaths in Africa and Asia for the foreseeable future. The immediate public health concern therefore is to establish VA methods for determining cause of death which are readily applicable on a large scale (including in routine CRVS processes) and provide sufficient detail for effective health planning.

Verbal autopsy interview material has been collected in a variety of ways, and then interpreted into cause of death data by various methods. There has therefore been substantial methodological heterogeneity involved, which can magnify existing uncertainties over cause–specific mortality. The World Health Organization (WHO) released a new standard for VA data collection together with a revised set of cause of death categories (with equivalence to the International Classification of Diseases version 10 [ICD–10]) in 2012 [7]. The process undertaken to streamline previous VA approaches into the new 2012 WHO VA standard is described in detail elsewhere [5].

Ways of interpreting VA data essentially fall into physician consideration of individual cases (physician–coded verbal autopsy, PCVA) or various mathematical approaches to automated processing of VA data. PCVA has been a *de facto* standard in many research settings, although associated details of methods and validity have not always been well established [8] other than in specific studies of hospital–based deaths. PCVA is generally considered too slow and expensive for routine CRVS implementation, apart from the disadvantage of consuming often scarce physician time. A number of approaches to automated processing have been tried over the last decade or so; the currently most widely used is the InterVA suite of models that apply Bayesian probabilistic modelling, and which have been in the public domain in various versions since 2005 (at www.interva.net) [9]. Corresponding to the release of the 2012 WHO VA standard, InterVA–4 was released in 2012, incorporating exactly the same range of input and output parameters as specified by WHO [10].

Nevertheless, monitoring cause–specific mortality is a long–term process, and so much of the existing VA material which is archived in various places reflects earlier standards and variations. It will be some time yet before any substantial body of VA data originally collected according to the provisions of the 2012 WHO VA standard becomes available. Our aim in this paper is to take VA archives from a variety of pre–2012 sources, which have also been assessed by PCVA, convert them insofar as is possible into the 2012 WHO format, and compare the PCVA and InterVA–4 findings. Our objective is primarily methodological. Rather than attempting to illuminate specific epidemiological findings, we evaluate the consistency between applying the 2012 WHO VA standard and the corresponding InterVA–4 model to existing secondary data, and compare this with the primary physician–coded findings from the same data. The underlying consideration is the public health consistency and relevance of the two approaches – InterVA–4 and PCVA – as a source of information for health planning in regions where routine cause–specific mortality data are scarce. Many national and regional public health practitioners are posing the question as to whether they can reasonably rely on verbal autopsy surveillance with automated methods for assigning cause of death to monitor mortality patterns in the populations they serve: this study aims to answer that question.

DATA SOURCES AND METHODS

For the purposes of this comparison, we have selected several VA data sets for secondary analyses on grounds of availability, variety of original VA procedures, coverage of diverse geographic locations and population groups, and with well–established local PCVA procedures. PCVA procedures varied slightly between sites, but for every site the consensus "main" or "underlying" cause was used here. The sources and characteristics of the data are shown in Table 1. Data were sourced from Afghanistan, Bangladesh, Ghana, Kenya and South Africa. The original sources were of two main types, Demographic and Household Surveys (DHS) [17] and INDEPTH Network Health and Demographic Surveillance Systems (HDSS) [18] but there were also local variations in the details of VA procedures used within these two groupings. The locations also cover a wide range of HIV and malaria prevalences, which are the two causes of death which vary most markedly geographically. The two sites in South Africa are only 600 km apart and share a number of characteristics, but used different VA procedures. All of the PCVA results were reported using ICD–10 codes, enabling direct comparison with the InterVA–4 outputs using the WHO 2012 ICD–10 cause category definitions.

Stata command files were created for each site to extract as many as possible of the 2012 WHO InterVA indicators for each case (possible indicators total 244 across all age–sex groups, with the number of applicable questions for any particular death ranging from 54 to 181) from the various VA data sets. VA records which did not contain any symptom data (ie, only identification and background indicators) or which did not include valid age and sex details were excluded. The VA data from each source were then processed using InterVA–4 (version 4.02) and the cause of death outputs processed into cause–specific mortality fractions (CSMF) as previously described [10]. PCVA outputs, specified as ICD–10 codes, were categorised into the 2012 WHO VA cause of death groups for comparative purposes,

using the conversion table specified in the WHO documentation. Age–groups corresponding to WHO 2012 categories (0–28 days, 1–11 months, 1–4 years, 5–14 years, 15–49 years, 50–64 years and 65+ years) were used as the basis for analysis. Because of inherent uncertainty at the individual level in differentiating in many cases between the 01.03 HIV/AIDS and 01.09 pulmonary TB cause categories, both for InterVA–4 and PCVA, comparisons are presented with those categories separate and combined.

CSMFs were calculated for each source and cause of death, separately for InterVA–4 and PCVA findings. Concordance between InterVA–4 and PCVA CSMFs was measured using Lin's concordance correlation coefficient [19], corrected and implemented for Stata [20]. As an alternative metric for assessing the equivalence of CSMFs from InterVA–4 and PCVA findings, we used the Wilcoxon matched–pairs signed ranks test and its two one–sided tests (TOST) variant for stochastic equivalence, with epsilon set to 3, as implemented for Stata [21]. Ratios of CSMFs according to InterVA–4 and PCVA, by source, age–sex group and cause, were calculated together with 99% CIs, according to the Katz adjusted log method which permits the estimation of intervals around ratios where one side is zero [22]. CIs were calculated at the 99% level as hundreds of separate ratios were assessed. The objective of calculating these CIs was not so much for the sake of demonstrating statistical significance, but rather to identify particular causes and age–sex groups for which the CSMF ratios between interpretations by InterVA–4 and physicians were appreciably lower or higher than might be expected by chance, taking into account the number of cases involved.

No specific ethical clearance was required for this study, which relied solely on the analysis of existing secondary data, without individually identifiable information. For the Kenya data set, in Kisumu, following cultural customs, compound heads provide written consent for all compound members to participate in the HDSS activities. Any individual can refuse to participate at any time. The Kisumu

Table 1. Characteristics of the six data sources used

Source	Type of data	Location	Population group	Period deaths occurred	Verbal autopsy instrument	Deaths covered	Reference
Afghanistan	DHS	National cluster sample survey	Entire	2005–2010	DDHS form	3349	[11]
Bangladesh	DHS	National cluster sample survey	Women aged 12 to 49 y	1997–2001	DHS form	928	[12]
Ghana	DHS	National cluster sample survey	Women aged 12 to 49 y	2002–2007	DHS form	4203	[13]
Kenya	INDEPTH HDSS	Surveillance site in Siaya County	Entire	2003–2010	Adapted INDEPTH form	21 236	[14]
South Africa A	INDEPTH HDSS	Surveillance site in Bushbuckridge	Entire	1992–2010	Locally adapted form	10 139	[15]
South Africa B	INDEPTH HDSS	Surveillance site in Kwa–Zulu Natal	Entire	2000–2011	Adapted INDEPTH form	14 327	[16]

DHS – Demographic and Health Survey, HDSS – Health and Demographic Surveillance System

HDSS protocol and consent procedures, including surveillance and VA, were approved by KEMRI and CDC Institutional Review Boards annually. For the South Africa A data set, surveillance–based studies in the Agincourt subdistrict were reviewed and approved by the Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand, Johannesburg, South Africa (protocol M960720, renewed). Informed consent was obtained at the individual and household levels at every follow–up visit, whereas community consent from civic and traditional leadership was secured at the start of surveillance and reaffirmed from time to time. For the South Africa B data set, ethical approval for the Africa Centre Demographic Surveillance was provided by the University of Kwa–Zulu–Natal Bio–Medical Research Ethics Committee (protocol E009/00).

RESULTS

Over the total of 54 182 VA records analysed, **Table 2** shows concordance correlation coefficients by data source and by age–group, both for the basic outputs and with the HIV and TB categories combined for sub–Saharan Africa. **Figure 1** shows, for each WHO 2012 cause category and over all the six sources, a scatter plot of CSMFs from both InterVA–4 and PCVA interpretations. The corresponding concordance correlation coefficient was 0.831 (95% CI 0.751–0.911), and this increased to 0.974 (95% CI 0.961–0.987) when the 01.03 HIV/AIDS and 01.09 pulmonary TB cause categories were combined for sub–Saharan Africa. **Table 3** shows results from the alternative Wilcoxon's metric for equivalence between CSMFs. Equivalence is represented by the large p values for the standard Wilcoxon's signed rank test (not permitting rejection of the null hypothesis of no difference) together with significant p values indicating that differences lay within the equivalence range.

Graphical presentations for each source separately, in a similar format to **Figure 1**, are available in **Online Supplementary Document**, which also show WHO 2012 cause categories. **Table 4** shows the CSMF for each WHO 2012 cause category and site, as determined by InterVA–4 and PCVA.

Using the CSMFs shown in **Table 3** for each cause and source, CSMF ratios InterVA–4:PCVA were calculated with 99% confidence intervals as a basis for comparison. These are tabulated fully in Additional File 1. Of the 320 source/ cause comparisons that were made, 171 (53.4%) of these
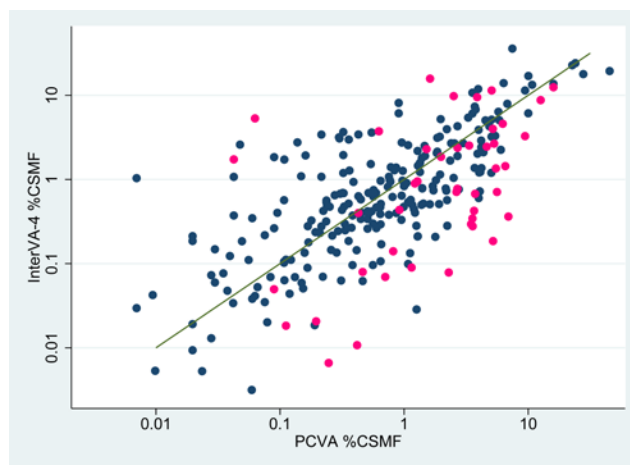
Figure 1. Correlation for cause–specific mortality fractions (CSMF) for WHO 2012 causes of death from six data sources, as determined by InterVA–4 [10] and physician–coded verbal autopsy (PCVA) for 54 182 verbal autopsies, against the line of equivalence. Pink markers represent residual cause categories; blue markers represent specific causes.

Table 2. Concordance correlation coefficients (CCC) for InterVA–4 [10] and physician–coded verbal autopsy (PCVA) interpretations of 54 182 verbal autopsies from 6 sources

	Deaths	Basic data		HIV/AIDS and pulmonary TB categories combined	
		CCC	95% CI	CCC	95% CI
Overall	54 182	0.831	0.751–0.911	0.974	0.961–0.987
Source:					
Afghanistan	3349	0.625	0.464–0.787	–	–
Bangladesh	928	0.720	0.580–0.860	–	–
Ghana	4203	0.665	0.509–0.821	0.751	0.631–0.871
Kenya	21 236	0.854	0.785–0.923	0.923	0.885–0.960
South Africa A	10 139	0.912	0.868–0.956	0.947	0.922–0.972
South Africa B	14 327	0.588	0.415–0.760	0.990	0.985–0.995
Age–group:					
0–28 d	1678	0.529	0.258–0.801	0.529	0.258–0.801
1–11 mo	5070	0.813	0.722–0.904	0.810	0.713–0.908
1–4 y	5123	0.886	0.824–0.948	0.909	0.857–0.961
5–14 y	1734	0.828	0.733–0.922	0.888	0.826–0.949
15–49 y	24 478	0.771	0.663–0.880	0.991	0.986–0.996
50–64 y	6239	0.784	0.667–0.902	0.981	0.969–0.993
65+ years	9860	0.846	0.760–0.931	0.895	0.835–0.956

CI – confidence interval, TB - tuberculosis

Table 3. Statistical analysis of ranked cause-specific mortality fractions, overall and by source, using the Wilcoxon matched–pairs signed ranks test and its two one–sided tests variant for stochastic equivalence

SOURCE	WILCOXON MATCHED PAIRS SIGNED RANKS (P)	TWO ONE–SIDED TESTS VARIANT FOR STOCHASTIC EQUIVALENCE ($\varepsilon = 3$) P_{LOW}, P_{HIGH}
Overall	0.187	0.001, 0.047
Afghanistan	0.808	0.001, 0.003
Bangladesh	0.870	0.002, 0.001
Ghana	0.358	0.001, 0.007
Kenya	0.607	0.001, 0.007
South Africa A	0.262	0.001, 0.030
South Africa B	0.509	0.001, 0.010

ratios were not significantly different from unity at the 99% level.

CSMFs were similarly calculated by age–group and sex, across all sources. These results, in a similar format to **Table 2**, are shown in **Online Supplementary Document**. A further table in **Online Supplementary Document** shows CSMF ratios InterVA–4:PCVA, with 99% confidence intervals, for each cause and age–sex group, over all data sources. Of the 530 age–sex/cause comparisons that were made, 329 (62.1%) of these ratios were not significantly different from unity at the 99% level.

DISCUSSION

Our results show a generally good level of agreement between the InterVA–4 and PCVA approaches to the interpretation of this large VA data set, over diverse populations. There are some important differences, discussed below, but nevertheless the two approaches achieved good public health equivalence, meaning that taking public health and health planning measures on the basis of either source would lead to similar conclusions. This concept of "public health equivalence" is very important in interpreting these findings. Development of VA methods in recent years has led to a situation in which public health practitioners in countries where deaths are not routinely registered with causes are posing important practical questions. They need to know whether they can reasonably rely on modern VA methods with automated interpretation to provide policy–relevant information on mortality patterns in a cost–effective manner. This is not just a matter of identifying major causes of death – it is equally critical, for example, to monitor causes that have become rare, such as measles, in order to be sure of the continued effectiveness of vaccination programmes. Previous work [23,24] has shown that InterVA–4 can be effectively operationalised at much lower cost than PCVA; here we demonstrate its functional equivalence to PCVA.

It is critical to realise that neither InterVA–4 nor PCVA, nor indeed the underlying VA data to which they have been applied, necessarily represent absolute truth (whatever that may be) in terms of cause of death. Cause of death assignment is, at best, a mixture of science and judgement [25]. There is an extensive literature on comparisons between different methods for determining cause of death, which show substantial inter–method variations. A review of clinical cause of death assignment and post–mortem findings found rates of discrepancies ranging from 30% to 63% across the 18 included studies [26]. Pre–mortem CT imaging has been evaluated as only able to correctly identify 66% of post–mortem examination causes of death [27]. In South Africa, an autopsy series on miners found that 51% of respiratory infections diagnosed at autopsy had not been noted clinically [28]. There is a clear need to improve future VA methods by validating causes of death directly against post–mortem findings, but that is a major undertaking given the widespread lack of autopsies undertaken in Africa and Asia [29]. Against this background of high discrepancy rates between post–mortem findings and other methods of assigning cause of death, the relatively good agreement between PCVA and InterVA–4 findings here is encouraging, even though both might differ from post–mortem findings if those were available.

Attempts have been made to validate VA approaches in specific studies with hospital or laboratory data [30]. Some specific causes of death are amenable to this approach, for example by using particular data sets where *ante–mortem* HIV or sickle–cell status is documented [31,32]. A study from the Population Health Metrics Research Consortium recruited tertiary facility deaths across a range of hospital–assigned pre–determined causes, which were followed up with VA interviews [33]. This data set was used to build new models for assigning cause of death, which were then tested together with other models and physician assigned causes in the same data set. Unsurprisingly, models built within this data set performed better in relation to the hospital causes than either other models or physicians [34]. Further bench–testing of VA interpretation models showed roughly equivalent performance across various models when compared to PCVA as the reference standard [35]. By defining performance in relation to PCVA, however, these evaluations precluded comparison of public health consistency between models and physicians.

Analytical methods for comparing cause of death assignment are not entirely straightforward, because of the general uncertainty associated with cause of death, the interplay between precipitating and underlying causes, and the nature of the data. Here we have concentrated on comparing CSMFs, since that is the primary outcome of interest from cause of death data in public health. The concordance correlation coefficients and rank equivalence tests used here present accessible and convenient summary measures of how CSMFs from two different sources compared. For in-

Table 4. Cause–specific mortality fractions from 54 182 verbal autopsies, by WHO 2012 virtual autopsy cause category and data source

CAUSE OF DEATH	DATA SOURCE											
	Afghanistan (3349 deaths)		Bangladesh (928 deaths)		Ghana (4203 deaths)		Kenya (21 236 deaths)		South Africa A (10 139 deaths)		South Africa B (14 327 deaths)	
	Inter-VA–4*	PCVA	Inter-VA–4	PCVA	Inter-VA–4	PCVA	Inter-VA–4	PCVA	Inter-VA–4	PCVA	Inter-VA–4	PCVA
01.01 Sepsis (non–obstetric)	0.26	0.09			0.01		0.24	0.19	0.19	0.02	0.02	
01.02 Acute resp. infect, incl. pneumonia	11.41	9.44	3.41	0.22	0.74	2.19	13.95	6.34	11.86	3.96	6.37	5.75
01.03 HIV/AIDS related death	0.89		0.12		22.73	22.65	17.85	27.82	24.09	24.01	19.41	45.33
01.04 Diarrhoeal diseases	5.06	5.85	1.37	4.20	1.20	5.04	2.41	4.19	2.02	3.91	0.57	2.22
01.05 Malaria	0.40	1.22	0.96	0.65	2.25	6.02	13.66	15.98	0.50	1.38	0.42	0.22
01.06 Measles	0.72						0.69	0.32	0.07		0.05	
01.07 Meningitis and encephalitis	2.51	1.46	1.52	0.54		3.55	0.76	2.76	0.51	1.91	1.04	2.51
01.08, 10.05 Tetanus							0.01	0.02		0.01		
01.09 Pulmonary tuberculosis	10.73	3.55	6.79	3.77	7.34	3.71	13.33	10.76	16.98	10.04	35.85	7.45
01.10 Pertussis	0.13						0.03		0.26		0.03	
01.11 Haemorrhagic fever	0.06						0.01		0.01	0.01		
01.99 Other and unspecified infect dis	1.35	5.49	0.34	3.56	0.19	5.21	0.95	1.28	0.68	3.74	0.14	0.82
02.01 Oral neoplasms	0.35	0.06	1.19	0.32	0.46	0.00	0.14		0.21	0.02	0.11	0.06
02.02 Digestive neoplasms	2.90	4.18	6.07	3.56	3.42	0.43	1.90	1.47	2.75	0.96	1.40	0.78
02.03 Respiratory neoplasms	1.84	0.09	1.95	0.32	2.59	0.05	1.72	0.11	0.56	0.24	1.93	0.16
02.04 Breast neoplasms	0.47	0.60	2.55	1.08	2.18	1.28	0.07	0.22	0.68	0.31	0.23	0.21
02.05, 02.06 Reproductive neoplasms M,F	0.49	0.24	4.29	2.69	3.61	0.55	0.33	0.95	0.98	1.80	0.98	0.77
02.99 Other and unspecified neoplasms	2.53	3.34	2.45	4.63	0.28	3.57	2.29	1.52	1.85	1.98	0.90	1.22
03.01 Severe anaemia	0.78		1.08	0.22	0.05		0.28	2.23	0.09		0.24	
03.02 Severe malnutrition	3.95	2.21	0.68		0.04		0.72	4.07	0.50	1.16	0.39	0.52
03.03 Diabetes mellitus	1.21	4.03	1.39	0.86	0.13	1.12	0.57	1.13	1.80	1.39	1.68	2.35
04.01 Acute cardiac disease	0.83	1.70	1.90	2.69	0.47	0.64	0.37	0.04	0.43	0.32	0.44	1.20
04.03 Sickle cell with crisis					0.18		0.27	0.38				
04.02 Stroke	4.28	4.87	7.92	6.79	1.23	4.12	1.23	1.34	2.10	4.36	3.30	5.42
04.99 Other and unspecified cardiac dis.	3.27	9.44	9.49	3.88	4.58	6.23	3.74	0.63	2.66	5.32	3.99	5.19
05.01 Chronic obstructive pulmonary dis.	1.58	1.34	0.10	0.11	0.24	0.00	0.60	3.99	2.76	0.14	1.28	0.36
05.02 Asthma	1.29	0.84	0.78	1.40	6.11	0.90	0.34	0.45	0.69	0.33	0.69	0.52
06.01 Acute abdomen	2.98	0.36	3.66	0.32	8.12	0.90	3.07	0.30	1.09	0.15	1.04	0.01
06.02 Liver cirrhosis	0.75	0.57	3.88	3.99	0.78	2.17	0.63	0.57	0.52	1.43	0.28	1.26
07.01 Renal failure	0.26	0.51	3.23	1.94	1.27	0.98	0.47	0.99	0.14	0.41	0.51	0.65
08.01 Epilepsy	0.40	0.87	1.46	1.29	0.03	1.26	0.17	0.65	0.30	0.56	0.40	0.45
98 Other and unspecified NCD	0.78	2.69	2.38	2.69	0.36	6.92	1.73	0.04	0.71	2.64	0.08	2.29
10.06 Congenital malformation	0.51	1.61		0.11			0.07	0.13	0.06	0.46	0.15	0.26
10.01 Prematurity	2.14	1.85					0.10	0.56	0.82	0.74	0.10	0.38
10.02 Birth asphyxia	3.17	0.30					0.93	0.39	0.53	0.24	0.24	0.29
10.03 Neonatal pneumonia	5.21	1.97					1.07	0.04	0.65	0.28	0.47	0.25
10.04 Neonatal sepsis	1.37	3.70					0.21	1.29	0.12	0.04	0.07	0.03
10.99 Other and unspecified neonatal CoD	1.44	6.54					0.40	0.43	0.08	0.46	0.02	0.11
12.01 Road traffic accident	2.70	2.99	0.28	0.22	2.06	1.83	0.42	0.51	2.43	2.69	2.69	2.39
12.02 Other transport accident		0.06				0.02				0.01		0.70
12.03 Accid. fall	0.64	0.96		0.11	0.42	0.55	0.22	0.08		0.10	0.04	0.06
12.04 Accid. drowning and submersion	0.62	0.81	0.11	0.65	0.30	0.33	0.33	0.18	0.14	0.29	0.25	0.34
12.05 Accid. expos to smoke, fire & flame	0.26	0.60	0.29	0.65	0.09	0.17	0.22	0.26	0.37	0.38	0.28	0.17
12.06 Contact with venomous plant/animal	0.34	0.51	0.97	0.97	0.40	0.52	0.11	0.12		0.09	0.08	0.03
12.10 Exposure to force of nature		0.06				0.32	0.04	0.01		0.15		0.03
12.07 Accid. poisoning and noxious subs	0.04	0.12	0.03		0.02	0.19	0.06	0.31	0.13	0.16	0.05	0.15
12.08 Intentional self–harm	0.48	0.33	6.12	10.02	0.40	0.10	0.32	0.24	0.79	1.40	0.94	0.77
12.09 Assault	3.13	1.85	0.38	0.75	0.52	0.36	0.69	0.59	2.69	2.54	5.14	5.07
12.99 Other and unspecified external CoD	0.29	3.46		1.83		0.31	0.09	1.15	0.44	0.92	0.07	0.70
09.01 Ectopic pregnancy			0.11	0.11	0.63	0.43	0.01		0.01	0.02	0.03	0.01
09.02 Abortion–related death	0.06	0.03	0.54	1.08	1.14	1.95	0.03	0.08		0.06	0.01	0.03
09.03 Pregnancy–induced hypertension	0.58	0.45	5.04	4.53	0.21	1.28	0.05	0.04	0.06	0.11	0.11	0.11
09.04 Obstetric haemorrhage	0.91	1.05	3.23	5.06	5.43	3.28	0.18	0.17	0.18	0.05	0.07	0.08
09.05 Obstructed labour	0.06	0.15	0.10	1.08	0.39	0.64						
09.06 Pregnancy–related sepsis	0.15	0.03	1.08	0.75	0.83	1.00	0.05	0.07	0.02	0.08	0.03	0.04
09.07 Anaemia of pregnancy	0.04	0.06	0.74	1.72	0.21	1.78	0.04		0.02	0.02	0.03	
09.08 Ruptured uterus			0.57	0.11	0.19	0.36		0.01				0.01
09.99 Other and unspecified maternal CoD	0.01	0.42	0.71	5.60	0.42	3.66	0.05	0.09	0.01	0.25	0.02	0.20
99 Indeterminate	11.41	5.08	8.76	12.61	15.77	1.62	9.77	2.51	12.45	15.99	5.32	0.06
Overall	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

VA – verbal autopsy, PCVA – physician–coded verbal autopsy, M – male, F – female, CoD – cause of death
*InterVA–4 software [10].

Verbal autopsy cause of death findings in Africa and Asia as determined by physician coding and probabilistic modelling

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dividual cause comparisons by factors such as source, age–group and sex, the ratio between CSMFs by the two methods provides insight on specific aspects for comparison, and the confidence interval of that ratio is informative in deciding whether or not differences are due to chance. It has been suggested that comparisons between cause of death methods should be corrected for chance agreement, which is more likely to occur in common causes [36]. However, from a public health perspective this is not necessarily appropriate, since in practice agreement is generally accepted irrespective of the possibility that it was derived by chance.

The overall size and geographic diversity of the data presented here are important attributes. These VA data were not collected under carefully controlled and standardised procedures in order to minimise real–life sources of variation; this is a major strength of this study. The sources deliberately included a mix of high and low HIV and malaria settings, which are the two causes of highest variation in CSMF findings between specific settings. In any cause of death data, a relatively small number of more common causes account for the majority of the deaths, followed by many causes accounting for small fractions in the remainder. Consequently it is only possible to evaluate cause of death methods thoroughly in data sets which are large enough to include realistic numbers of rarer causes. Globally, most unrecorded deaths occur in Africa and Asia, which are therefore the regions where VA methods are most urgently needed, and which are represented in these data. It must also be noted that inevitably none of these archived data sets were originally collected under the WHO 2012 VA standard, and hence some degree of inter–site variation may have been introduced in the process of extracting the necessary VA indicator data.

One commonly contentious area in terms of cause of death is the interaction between HIV/AIDS and pulmonary TB. Three of the six data sources included substantial numbers of HIV/AIDS deaths during the periods covered by these data, and both InterVA–4 and PCVA findings reflected that. A validation study for InterVA–4 in relation to HIV sero–status showed high specificity for HIV/AIDS as a cause of death (ie, relatively few false–positive HIV/AIDS cause assignments) but also showed considerably elevated mortality rates among sero–positives for causes such as pneumonia and pulmonary tuberculosis [31]. Although ICD–10 coding in principle requires the use of codes B20–B24 where HIV and co–infections are involved, the extent to which this can reliably be implemented using VA methods is debatable, particularly if VA respondents are unaware of the HIV status of the deceased. In these analyses, there are clear differences between the two South African sources in this respect, with appreciably different proportions of deaths assigned as HIV/AIDS or tuberculosis. Conversely, in low HIV/AIDS or malaria settings, physicians may be reluctant to assign deaths to those causes. For example in the Afghan data set, where very few HIV/AIDS deaths might be expected, HIV/AIDS was explicitly mentioned in four VA interviews, but this was not reflected in the PCVA results, which never assigned HIV/AIDS as a cause of death.

Any cause of death assignment process, at the individual level, will involve some degree of uncertainty. Formal procedures for assigning cause of death, for example in official death certificates, do not generally capture this uncertainty, but require the certifier to make a clear choice between possible causes [8]. Even if two certifiers are required to assess a case independently, as is often practised in PCVA, agreement does not necessarily constitute truth. One factor that emerges clearly from these analyses is that in the PCVA findings there is a greater tendency for physicians to choose chapter residual categories (pink markers in **Figure 1**), rather than specific causes (blue markers in **Figure 1**). This is evident from most of the pink markers lying below the line of equivalence, and is probably an expression of PCVA uncertainty. This was particularly evident in the neonatal age group, in addition to cross–over between neonatal sepsis and pneumonia categories, as seen in **Online Supplementary Document**, Table s2, resulting in the lower correlation observed for neonates. On the other hand, InterVA–4, by using a probabilistic model, computes a residual uncertainty for each case which is then expressed as an indeterminate component. By expressing uncertainty in this way, CSMFs for indeterminate causes may be greater according to InterVA–4.

CONCLUSIONS

Given the inherent difficulties and uncertainties involved in assigning cause of death, and the urgent need to implement large–scale, cost–effective CRVS procedures that include cause of death, it is clear that the priority for the foreseeable future in many low– and middle–income countries will be to undertake VA with automated cause of death assignment. We have shown here, using a large and diverse data set, that there is a strong correlation between in–country PCVA findings and outputs from the freely available InterVA–4 model, over a wide range of settings. Whilst accepting that neither PCVA nor InterVA–4 results necessarily represent absolute truth, and that there is a continuing search for improved methods for assigning causes of death, the use of InterVA–4 represents a low–resource and highly consistent strategy, which is a major advance on knowing almost nothing about cause of death profiles in many populations. The diversity of cause of death profiles which InterVA–4 produces across the various sources clearly demonstrates that a standard model can be used successfully over a wide range of settings. InterVA–4, and the WHO 2012 VA standard with which it is fully compatible, should therefore be used as the currently available tools of choice for filling gaps in cause–specific CRVS data.

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Unemployment, public–sector health care expenditure and HIV mortality: An analysis of 74 countries, 1981–2009

Mahiben Maruthappu[1], Charlie Da Zhou[2], Callum Williams[3,4], Thomas Zeltner[5,6], Rifat Atun[7]

[1] Imperial College London, London, UK

[2] New College, University of Oxford, Oxford, UK

[3] The Economist, London, UK

[4] Faculty of History, University of Oxford, Oxford, UK

[5] Special Envoy for Financing to the Director General of the World Health Organization, Geneva, Switzerland

[6] University of Bern, Bern, Switzerland

[7] Harvard School of Public Health, Boston, MA, USA

Background The global economic downturn has been associated with increased unemployment and reduced public–sector expenditure on health care (PSEH). We determined the association between unemployment, PSEH and HIV mortality.

Methods Data were obtained from the World Bank and the World Health Organisation (1981–2009). Multivariate regression analysis was implemented, controlling for country–specific demographics and infrastructure. Time–lag analyses and robustness–checks were performed.

Findings Data were available for 74 countries (unemployment analysis) and 75 countries (PSEH analysis), equating to 2.19 billion and 2.22 billion people, respectively, as of 2009. A 1% increase in unemployment was associated with a significant increase in HIV mortality (men: 0.1861, 95% CI: 0.0977 to 0.2744, $P < 0.0001$, women: 0.0383, 95% CI: 0.0108 to 0.0657, $P = 0.0064$). A 1% increase in PSEH was associated with a significant decrease in HIV mortality (men: –0.5015, 95% CI: –0.7432 to –0.2598, $P = 0.0001$; women: –0.1562, 95% CI: –0.2404 to –0.0720, $P = 0.0003$). Time–lag analysis showed that significant changes in HIV mortality continued for up to 5 years following variations in both unemployment and PSEH.

Interpretation Unemployment increases were associated with significant HIV mortality increases. PSEH increases were associated with reduced HIV mortality. The facilitation of access–to–care for the unemployed and policy interventions which aim to protect PSEH could contribute to improved HIV outcomes.

Correspondence to:

Mahiben Maruthappu
Faculty of Arts and Sciences
Harvard University
Cambridge, MA 02138
USA
maruthappu@post.harvard.edu

The recent economic downturn has had profound effects on an international scale. Governmental responses around the world have included the introduction of radical austerity measures in an attempt to reduce budget deficits by increasing taxation while cutting back expenditure [1,2]. These fiscal policies have resulted in unprecedented rises in unemployment rates [3-5] which has coincided with a period of slower than expected growth in public–sector expenditure on health care (PSEH) [6,7]. For example, in the 33 countries of the Organisation for Economic Co–operation and Development (OECD), which collectively account for more than 1.24 bil-

lion individuals, unemployment levels rose from 5.6% to 7.6% following the recession [5]. In the United States, the recession preceded the lowest annual growth in PSEH in fifty years [7]. Concurrently, there has been a substantial slowdown in the growth of internationally sourced funding for development assistance in health [8]. Such changes have raised the question of how economic changes, both within and outside of crises, impact population health.

There are widespread concerns about the potential detriment that the current economic environment may have on global public health [9]. The adverse effects of economic crises on population health outcomes, including all–cause mortality, suicide rates and mental health, have been well described [10]. These trends have also been confirmed in the context of the current recession [11-13]. The role of unemployment, specifically, in the perpetuation of a variety of unhealthy phenomena has also been confirmed [14-19]. The contribution of PSEH on population health has been shown to be modest when compared to other variables, such as sanitation and nutrition [20, 21]. PSEH does, however, seem to disproportionately benefit the poorer substrata within populations [22]. It would follow that reduced PSEH at times of increased unemployment would serve to exacerbate negative health outcomes. Despite these findings, detailed analyses of the relationship between unemployment and PSEH with specific pathologies have, by and large, been neglected.

Human immunodeficiency virus (HIV) is the leading cause of global mortality by a single pathogenic agent, predominantly affecting young adults of working age [23]. A small number of studies have investigated the effect of financial downturns on HIV–infected individuals in single country settings, concluding that unemployment is an independent risk factor for disease progression and mortality [24, 25]. However, population–wide correlations at the multinational level, in addition to long–term trends, have yet to be determined.

In this study, we sought to evaluate the association between unemployment, PSEH, and HIV mortality in 74 and 75 countries, respectively, between 1981 and 2009 (**Table 1**). Given the current economic climate and pressures to develop appropriate policy responses, we believe this to be highly topical.

METHODS

Data collection

Annual national HIV mortality data, between 1981 and 2009, were obtained from the World Health Organisation's (WHO) mortality database [26]. The quality of this data has been evaluated by the WHO [27]. Reported national

death statistics were assessed by completeness, coverage and quality (**Online Supplementary Document**). Completeness was defined as the proportion of all deaths that are registered in the population covered by the vital registration system for a country. Coverage is calculated by dividing the total number of deaths reported from vital registration system for a country-year by the total number of deaths estimated by the WHO for that year for the national population. No adjustments have been made to the raw data to account for under-coverage. Quality was determined by taking into account the revision of the International statistical classification of diseases and related health problems (ICD) was used for national vital registration statistics, the completeness of data and minimal use of ill-defined categories of death. Of the 78 countries included in both of our analyses, data evaluation was not performed for 2 countries: Hong Kong and Porto Rico. Of those remaining, 67 countries had achieved completeness of greater or equal to 80% and 73 achieved completeness of greater or equal to 70%. 62 countries had coverage of greater or equal to 80% and 73 had coverage greater or equal to 70%. 20 countries were determined to have high quality data, 39 medium and 17 low.

As defined by the WHO, age standardised death rates (ASDR) is the weighted average of age–specific mortality rates per 100 000, where the weights are proportional to the number of persons in each corresponding age group of the WHO standard population [28]. ASDR per 100 000 was used as the basis of our statistical analysis as it controls for differences in age distribution within populations. Socioeconomic data were obtained from the World Bank's Development Indicators Database 2013 [29]. Unemployment was taken to be the proportion of the labour force without work but available and seeking employment, as defined by the World Bank [29]. PSEH data was measured as a percentage of national gross domestic product (GDP). It is defined by the World Bank to consist of recurrent and capital spending from government budgets, external borrowings, grants and social health insurance funds [29]. Data on 74 and 75 countries were available for the unemployment and PSEH analyses respectively (**Table 1**). As of 2012, this represented 2.19 billion and 2.22 billion people respectively.

Statistical analysis

Multivariate regression analysis was used to assess the relationship between HIV mortality (dependent variable) and unemployment and PSEH (independent variables). To ensure that results were not driven by extreme observations for certain countries, a fixed–effects approach was used in our regression models, including dummy variables for every country in the data set. Doing this meant that our model evaluated mortality changes within individual countries

Table 1. Countries included in our analysis

Country	Unemployment analysis	PSEH analysis	Country	Unemployment analysis	PSEH analysis
Albania	✔	✔	Lithuania	✔	✔
Argentina	✔	✔	Macedonia, FYR	✔	✔
Armenia	✔	✔	Mauritius	✔	✔
Australia	✔	✔	Mexico	✔	✔
Austria	✔	✔	Moldova	✔	✔
Azerbaijan	✔	✔	Montenegro	✘	✔
Bahrain	✔	✔	Netherlands	✔	✔
Belarus	✘	✔	New Zealand	✔	✔
Belgium	✔	✔	Norway	✔	✔
Bosnia and Herzegovina	✔	✘	Oman	✘	✔
Brazil	✔	✔	Panama	✔	✔
Bulgaria	✔	✔	Paraguay	✔	✔
Canada	✔	✔	Philippines	✔	✔
Chile	✔	✔	Poland	✔	✔
Colombia	✔	✔	Portugal	✔	✔
Costa Rica	✔	✔	Puerto Rico	✔	✘
Croatia	✔	✔	Qatar	✔	✔
Cuba	✔	✔	Romania	✔	✔
Cyprus	✔	✔	Russian Federation	✔	✔
Czech Republic	✔	✔	Serbia	✔	✔
Denmark	✔	✔	Singapore	✔	✔
Ecuador	✔	✔	Slovak Republic	✔	✔
Egypt, Arab Rep.	✔	✔	Slovenia	✔	✔
El Salvador	✔	✔	South Africa	✔	✔
Estonia	✔	✔	Spain	✔	✔
Finland	✔	✔	Sri Lanka	✔	✔
France	✔	✔	Sweden	✔	✔
Georgia	✔	✔	Switzerland	✔	✔
Germany	✔	✔	Thailand	✔	✔
Greece	✔	✔	Trinidad and Tobago	✔	✔
Guatemala	✔	✔	Ukraine	✔	✔
Hong Kong SAR, China	✔	✘	United Kingdom	✔	✔
Hungary	✔	✔	United States	✔	✔
Ireland	✔	✔	Uzbekistan	✘	✔
Israel	✔	✔	Uruguay	✔	✔
Italy	✔	✔	Venezuela, RB	✔	✔
Japan	✔	✔	**Total population (male)**	1 073 281 689	1 087 959 917
Kazakhstan	✔	✔	**Percentage of world population (male)**	30.22%	30.63%
Korea, Rep.	✔	✔	**Total population (female)**	1 121 036 031	1 135 056 068
Kuwait	✔	✔	**Percentage of world population (female)**	32.08%	32.48%
Kyrgyz Republic	✔	✔	**Total population (both sexes)**	2 194 317 721	2 223 015 985
Latvia	✔	✔	**Percentage of world population (both sexes)**	31.14%	31.55%

PSEH – public–sector expenditure on health care

while holding constant time–invariant differences between countries such as a higher predisposition to HIV, as well as political, cultural and structural differences. This conservative modelling approach made the data more comparable. The demographic structure of the selected countries was also controlled for by incorporating total population size and the proportions of the population that were aged over 65 and below 15 years into the model.

We used the Cook–Weisberg test [30] to assess for and to confirm heteroskedasticity (where sub–samples have different distributions) in the data used. Therefore, robust standard errors were included in the regression models; this allowed us to account for heterogeneity in unemployment and PSEH data due to differences in the way that countries measured unemployment rates and PSEH, along with factors such as underemployment or social programmes (for example, back–to–work initiatives or programmes that see people move from unemployment into education or training) that may otherwise have hidden or suppressed actual unemployment rates.

Due to the inclusion of several control variables (which in turn results in the loss of degrees of freedom and reduced sample size), our approach was highly conservative. This methodology has been widely used in similar health–economic studies and is regarded as a statistically robust approach [19, 31-35].

The fixed effects model used was as follows:

$$H_{i,t} - H_{i,0} = \alpha + (U_{i,t} - U_{i,0})\,\beta + \eta t + \varepsilon_{i,t}$$

Where i is country and t is year; H is the response variable or health measure (HIV mortality); U is the predictor variable (either unemployment or public–sector health care spending); α represents the population structure of the country being analysed; η is a dummy variable for each country included in the regression model; and ε is the error term. The coefficients of the control variables can be found in **Online Supplementary Document**.

We conducted 1–, 2–, 3–, 4– and 5–year time–lag multivariate analyses to quantify the long–term effects of changes in unemployment and PSEH on HIV mortality. To ensure the robustness of our findings, we conducted a series of further statistical analyses on the associations of unemployment and PSEH on HIV mortality in both sexes, taking into

consideration several additional control variables. First, we controlled for GDP per capita, inflation and national debt (as a percentage GDP). These markers of national economic well–being are commonly used as indicators for the standard of living and also influence national health care budgets. Second, we controlled for urbanisation, calorific intake and access to clean water. Our third robustness check combined the controls from the previous two. Fourth, we controlled for out of pocket health care expenses. Fifth, private health care expenditure (as a percentage GDP) was controlled for. Sixth, we controlled for changes in crude death rate; this accounted for mortality risk inherent to the unemployed and in countries with reduced government health care spending, allowing us to determine HIV–specific trends. Seventh, we re–ran the original multivariate regressions using data classified as either Level 1 or Level 2 in quality by the WHO. Finally, we reran the PSEH analysis with changes in PSEH measured in purchasing power parity (PPP) per capita rather than GDP. The association between both unemployment and PSEH and HIV mortality remained statistically significant ($P < 0.05$) throughout all of our robustness checks (**Table 2**).

Stata SE version 12 was used for the analysis (Stata Corporation, Texas, USA).

Table 2. Robustness checks

Robustness check	Controls used in multiple regression	Coefficient	P value	Lower confidence interval	Upper confidence interval
Multiple regression analyses were re–run using the controls in the original analysis (population size, proportion of population above 65 y of age, proportion below 14, and individual country controls), in addition to those mentioned in the table below. A 1% rise in unemployment remains statistically associated with increased HIV mortality in both sexes across all robustness checks:					
Economic controls	Original analysis controls and: changes in GDP per capita, inflation and government debt as a percentage of GDP	0.0957	0.0052	0.0287	0.1627
Infrastructure controls	Original analysis controls and: urbanisation, access to water and nutrition (mean calorific intake)	0.1781	<0.0001	0.1086	0.2475
Combined economic and infrastructure controls	Original analysis controls and: changes in GDP per capita, inflation, government debt as a percentage of GDP, urbanisation, access to water and nutrition (mean calorific intake)	0.1599	0.0004	0.0715	0.2483
Healthcare controls	Original analysis controls and: out of pocket expenses	0.1042	0.0109	0.0241	0.1843
	Original analysis controls and: private health expenditure as a percentage of GDP	0.1108	0.0069	0.0305	0.1910
Crude death rate controls	Original analysis controls and: crude death rate	0.1166	<0.0001	0.0607	0.1725
WHO data quality check	Original analysis controls, using WHO level 1 and 2 surveillance data only	0.1218	0.0001	0.0629	0.1807
Similarly, a 1% rise in public health expenditure remains statistically associated with decreased HIV mortality in both sexes across all robustness checks:					
Economic controls	Original analysis controls and: changes in GDP per capita, inflation and government debt as a percentage of GDP	–0.4369	0.0002	–0.6647	–0.2091
Infrastructure controls	Original analysis controls and: urbanisation, access to water and nutrition (mean calorific intake)	–0.3880	0.0007	–0.6110	–0.1649
Combined economic and infrastructure controls	Original analysis controls and: changes in GDP per capita, inflation, government debt as a percentage of GDP, urbanisation, access to water and nutrition (mean calorific intake)	–0.4104	0.0094	–0.7191	–0.1012
Healthcare controls	Original analysis controls and: out of pocket expenses	–0.3270	0.0004	–0.5065	–0.1475
	Original analysis controls and: private health expenditure as a percentage of GDP	–0.3225	0.0001	–0.4804	–0.1646
Crude death rate controls	Original analysis controls and: crude death rate	–0.2755	0.0015	–0.4450	–0.1061
WHO data quality check	Original analysis controls, using WHO level 1 and 2 surveillance data only	–0.3260	0.0001	–0.4841	–0.1679
Alternative PSEH measure	Rerun original analysis with PSEH measured in PPP per capita	–0.0009	<0.0001	–0.0012	–0.0006

GDP – gross domestic pruduct, WHO – World Health Organization, PSEH – public–sector expenditure on health care, PPP – purchasing power parity

PAPERS

RESULTS

The results of our regression analyses evaluating the effects of unemployment and PSEH on HIV mortality per 100 000, 1981–2009, controlling for inter–country differences in infrastructure and demographics, are shown in **Table 3**.

Unemployment

A 1% rise in unemployment was found to be associated with a statistically significant immediate rise in HIV mortality in both males (coefficient 0.1861, 95% CI: 0.0977 to 0.2744, $P < 0.0001$) and females (coefficient 0.0383, 95% CI: 0.0108 to 0.0657, $P = 0.0064$). As of 2012, the combined populations of the 74 countries in our analysis was in excess of 2.19 billion individuals.

Lag analysis showed that unemployment rises were associated with significantly increased HIV mortality for several years following the initial change (**Table 3**). In males, there is a significant association for 3 years after the rise in unemployment. In year 1, coefficient 0.1523, 95% CI: 0.0636 to 0.2411, $P = 0.0008$. In year 2, coefficient 0.1436, 95% CI: 0.0603 to 0.2270, $P = 0.0008$. And in year 3, coefficient 0.0964, 95% CI: 0.231 to 0.1697, $P = 0.0100$. After this interval, the association becomes non–significant. In females, the association remains statistically significant for at least 5 years. In year 1, coefficient 0.0345, 95% CI: 0.0082 to 0.0607, $P = 0.0101$. In year 2, coefficient 0.0446, 95% CI: 0.0190 to 0.0702, $P = 0.0007$. In year 3, coefficient 0.0395, 95% CI: 0.0141 to 0.0649, $P = 0.0123$. In year 4, coefficient 0.0352, 95% CI: 0.0077 to 0.0628, $P = 0.0123$. And in year 5, coefficient 0.0377, 95% CI: 0.0045 to 0.0709, $P = 0.0260$.

PSEH

The combined population of the 75 countries included in our PSEH analysis exceeded 2.22 billion individuals in 2012. A 1% rise in PSEH was found to be associated with a significant reduction in HIV mortality. Within the first year following a 1% increase in PSEH, the ASDR of HIV changed by a coefficient of –0.5015, 95% CI: –0.7432 to –0.2598, $P = 0.0001$ in males, and by a coefficient of –0.1562, 95% CI: –0.2404 to –0.0720, $P = 0.0003$ in females.

Lag analysis of the PSEH data showed that these associations with HIV mortality persisted for at least 5 years in males. For year 1, coefficient –0.5398, 95% CI: –0.8537 to –0.2258), $P = 0.0008$. In year 2, coefficient –0.4704, 95% CI: 0.7518 to –0.1890, $P = 0.0011$. In year 3, coefficient –0.5063, 95% CI: –0.7916 to –0.2210, $P = 0.0005$. In year 4, coefficient –0.4674, 95% CI: –0.7705 to –0.1642, $P = 0.0026$. And in year 5, coefficient –0.3511, 95% CI: –0.6507 to –0.0514, $P = 0.0218$. In females, the statistically significant association persisted for 4 years following the change in PSEH. For year 1, coefficient –0.2105, 95% CI: –0.3460 to –0.0749, $P = 0.0024$. In year 2, coefficient –0.1623, 95% CI: 0.2853 to –0.0393, $P = 0.0098$. In year 3, coefficient –0.1881, 95% CI: –0.3080 to –0.0682, $P = 0.0022$. In year 4, coefficient –0.1599, 95% CI: –0.2906 to –0.0292, $P = 0.0165$.

DISCUSSION

This study demonstrates that both increased unemployment and decreased PSEH are associated with increased HIV mortality on a global scale. Changes in these two pa-

Table 3. Multiple regression and lag analysis

Number of years after 1% rise in unemployment	Male HIV mortality per 100 000				Female HIV mortality per 100 000			
	Coefficient	P value	Lower confidence interval	Upper confidence interval	Coefficient	P value	Lower confidence interval	Upper confidence interval
Impact of a hypothetical 1% rise in unemployment on HIV mortality, controlling for proportion of population under the age of 14, proportion of population over the age of 65, population size and 74 country controls:								
Year 0 (year of change in unemployment)	0.1861	<0.0001	0.0977	0.2744	0.0383	0.0064	0.0108	0.0657
Year 1	0.1523	0.0008	0.0636	0.2411	0.0345	0.0101	0.0082	0.0607
Year 2	0.1436	0.0008	0.0603	0.2270	0.0446	0.0007	0.0190	0.0702
Year 3	0.0964	0.0100	0.0231	0.1697	0.0395	0.0023	0.0141	0.0649
Year 4	0.0551	0.1421	–0.0185	0.1288	0.0352	0.0123	0.0077	0.0628
Year 5	0.0621	0.1306	–0.0184	0.1425	0.0377	0.0260	0.0045	0.0709
The impact of a 1% rise in public health expenditure on HIV mortality, controlling for proportion of population under the age of 14, proportion of population over age of 65, population size and 75 country controls:								
Year 0 (year of change in unemployment)	–0.5015	0.0001	–0.7432	–0.2598	–0.1562	0.0003	–0.2404	–0.0720
Year 1	–0.5398	0.0008	–0.8537	–0.2258	–0.2105	0.0024	–0.3460	–0.0749
Year 2	–0.4704	0.0011	–0.7518	–0.1890	–0.1623	0.0098	–0.2853	–0.0393
Year 3	–0.5063	0.0005	–0.7916	–0.2210	–0.1881	0.0022	–0.3080	–0.0682
Year 4	–0.4674	0.0026	–0.7705	–0.1642	–0.1599	0.0165	–0.2906	–0.0292
Year 5	–0.3511	0.0218	–0.6507	–0.0514	–0.0620	0.2863	–0.1760	0.0521

rameters have an immediate association with changes HIV mortality which continues into the medium–term. The significance of these findings persisted even after consideration of a variety of potential confounders, including demographic, economic, infrastructure, health care, and data quality related factors.

Mechanisms

We propose a number of mechanisms that may underlie a potential causal link between unemployment and HIV mortality (**Figure 1**). First, unemployment may contribute towards the reduced socioeconomic status of HIV–infected individuals. A number of studies have previously shown that low socioeconomic status is associated with an increased risk of HIV mortality [36-39]. Some have concluded that this the result of reduced health care access which in turn results in delayed diagnosis and treatment [36]. Others suggest that an association remains even after consideration of such factors and instead propose that low socioeconomic status acts as an independent risk factor for HIV mortality [38].

Unemployment contributes towards the perceived barriers to health care access [40], and there is reduced utilisation of health care services by the unemployed compared to their employed counterparts [41]. Whether employment status impacts upon HIV mortality through delayed health care access [39] or is an independent risk factor is currently unclear [25]. Our study does, however, confirm this association across a global data set.

The influence of unemployment on impaired mental well-being [14, 16] and increased suicidal tendencies has been well described [11, 18, 19]. The psychological sequelae associated with unemployment may also contribute towards increased HIV mortality.
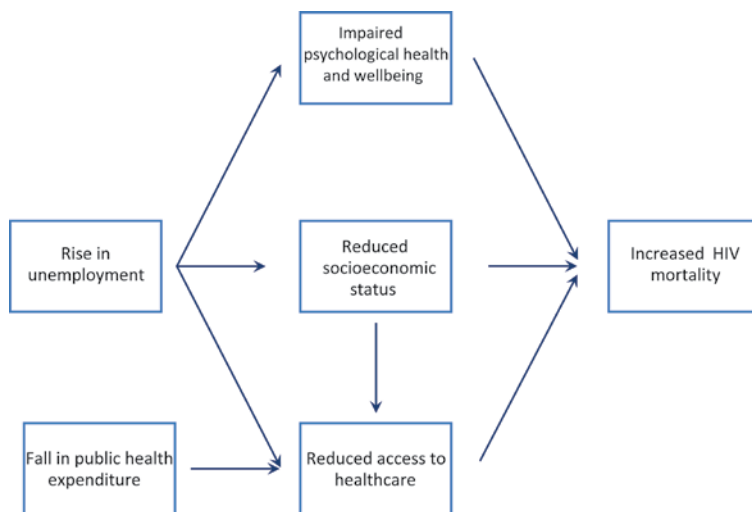
Figure 1. Mechanisms that may underlie a potential causal link between unemployment and HIV mortality.

Regarding PSEH, mechanisms are likely to focus on the availability of health care resources, which may be reduced during times of decreased PSEH. The era of highly active antiretroviral therapy (HAART) has seen vast improvements in HIV survival [42]. However, despite a gradual reduction in price, HAART remains an expensive therapeutic intervention. Importantly, better treatment outcomes of HAART are associated with the provision of free medication [43, 44]. It has also been shown that ineffective prophylaxis and treatment of co–morbidities, such as tuberculosis or opportunistic infections, can also contribute to higher HIV–mortality in low–income countries [44]. As a result both HIV–specific and general PSEH can have a direct impact upon HIV mortality.

It is likely that different mechanisms predominate in high–income and low–income settings. In high–income settings, the state tends to contribute towards the great majority to health care provision via PSEH, during times of recession there is also reduced long–term growth in private health insurance and out–of–pocket expenditure [7]. In lower–income countries, the contribution of the state is comparatively small and in the context of minimal private insurance cover, health care is funded primarily by out–of–pocket expenses [45]. As a result, economic crises can be particularly detrimental to health care access in such countries.

Limitations

The introduction of bias was minimised from this study by only using data from high–quality, objective, centralised databases. Sufficient data was collected to allow us to capture multinational associative trends.

We recognise, however, that there are potential limitations to our study. Our evaluation of annual national data would have limited our ability to capture variations at the subnational level or within intra–year time-frames. HIV mortality served as the endpoint of our study; as a result we will have overlooked the influence of unemployment and PSEH on other health measures. We were unable to stratify our study by socioeconomic class – a factor which is known to have a significant influence on health care outcomes [36-39]. While we show a statistical association between unemployment and PSEH with HIV mortality, a causal link cannot be established. While we did intend for our study to have a truly global scope, a number of countries were omitted due to inadequate data for HIV mortality, unemployment and PSEH. In particular, only two countries in sub–Saharan Africa (Mauritius and South Africa) were included in our analysis despite the disproportionate burden

of HIV in this region of the world. We also recognise that unemployment may not serve as an accurate barometer of individual financial well–being in less–developed countries. The poorest sub–strata within these populations may engage in work within the informal sector or in small–scale agriculture on subsistence farms. In such settings, government census data on employment status may be less meaningful. Our study is a retrospective, observational ecological study and so lacks the reliability of a prospective, experimental study. It may be subject to the influence of unknown or inadequately controlled confounders and cannot give strong evidence for causal attribution. Additional considerations, such as, indicators of political changes, occurrence of conflict or war, educational levels, and others, may permit any underlying mechanisms to be better determined. Further statistical techniques, such as interaction analyses could also provide insight into specific causal mechanisms. However, we believe this to be outside the immediate scope of this study which aimed to determine whether associations existed between the investigated variables.

Nevertheless, our study does establish an association between unemployment and PSEH with HIV mortality, thereby enabling a discussion of the trend on a supranational setting.

Implications

Our study suggests that macro–level multinational policy could potentially impact upon mortality at the level of the individual, affecting day–to–day clinical practice. Times of reduced government spending and increased unemployment are likely to have worsened HIV mortality. It is possible that recently implemented austerity measures which have been associated with such changes are exacerbating the adverse health effects of the global economic downturn rather than ameliorating them.

In the current environment, policies that act to promote return–to–work or which prevent further unemployment could have tangible benefits in terms of HIV survival. Previous retrospective OECD analyses have shown that certain factors, such as employment protection legislation and work–sharing programmes, can confer resilience against unemployment rises during times of economic hardship [5]. Such strategies that actively maintain aggregate employment levels may also serve to protect population health during future recessions.

Caution must be taken in debates concerning health care cost restrictions and budget restrictions. If cost reductions are not achieved as a result of improvements in efficiency, they may entail deterioration in the quality of care and in turn greater mortality. Given that increases in health care spending, at least in the immediate timeframe, are unlikely, maximization of health care value is necessary to maintain and improve upon current HIV outcomes [46, 47].

CONCLUSIONS

Recent economic turmoil has resulted in increased unemployment and decreased PSEH in countries around the world, raising the question of how economic changes, both within and outside crises, impact population health. Our study has shown that unemployment rises, and falls in PSEH, between 1981 and 2009, have been significantly associated with prolonged worsened HIV mortality. Policy interventions and austerity measures which negatively influence employment and PSEH may present additional barriers to HIV management.

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Understanding maternal mortality from top–down and bottom–up perspectives: Case of Tigray Region, Ethiopia

Hagos Godefay[1], Peter Byass[2,3,4], John Kinsman[2], Afework Mulugeta[5]

[1] Tigray Regional Health Bureau, Mekelle, Ethiopia

[2] Umeå Centre for Global Health Research, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

[3] Institute of Applied Health Sciences, School of Medicine and Dentistry, University of Aberdeen, Aberdeen, UK

[4] MRC/Wits Rural Public Health and Health Transitions Research Unit, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[5] College of Health Sciences, Mekele University, Mekele, Ethiopia

Background Unacceptably high levels of preventable maternal mortality persist as a problem across sub–Saharan Africa and much of south Asia. Currently, local assessments of the magnitude of maternal mortality are not often made, so the best available information for health planning may come from global estimates and not reflect local circumstances.

Methods A community–based cross-sectional survey was designed to identify all live births together with all deaths among women aged 15–49 years retrospectively over a one–year period in six randomly selected districts of Tigray Region, northern Ethiopia. After birth and death identification, Health Extension Workers trained to use the WHO 2012 verbal autopsy (VA) tool visited households to carry out VAs on all deaths among women aged 15–49 years. All pregnancy–related deaths were identified after processing the VA material using the InterVA–4 model, which corresponds to the WHO 2012 VA. A maternal mortality ratio (MMR) was calculated for each District and expressed with a 95% confidence interval (CI).

Results The MMRs across the six sampled Districts ranged from 37 deaths per 100 000 live births (95% CI 1 to 207) to 482 deaths per 100 000 live births (95% CI 309 to 718). The overall MMR for Tigray Region was calculated at 266 deaths per 100 000 live births (95% CI 198 to 350). Direct obstetric causes accounted for 61% of all pregnancy–related deaths. Haemorrhage was the major cause of pregnancy–related death (34%). District–level MMRs were strongly inversely correlated with population density ($r^2 = 0.86$).

Conclusion This simple but well–designed survey approach enabled estimation of maternal mortality in Tigray Region on a local, contemporary basis. It also provided insights into possible local variations in MMR and their determinants. Consequently, this approach could be implemented at regional level in other large sub–Saharan African countries, or at national level in smaller ones to monitor and evaluate maternal health service interventions.

Correspondence to:

Hagos Godefay
Head, Tigray Regional Health Bureau
Mekele
Ethiopia
hgodefay@yahoo.com

Maternal mortality is one of the most sensitive indicators of the health disparities between poorer and richer nations, but also one of the most difficult health outcomes to measure reliably. Many estimation exercises

and much debate have occurred around persistently unacceptable levels of maternal mortality in the world's poorer countries, not least in relation to the fifth Millennium Development Goal (MDG5) [1]. However, in many settings major challenges remain in terms of both reducing and measuring maternal mortality effectively.

In an ideal world, all maternal deaths would be routinely registered, but in reality civil registration of deaths with cause is extremely scanty in sub–Saharan Africa and south Asia, where most maternal deaths occur [2]. Consequently global estimates from the UN agencies [3-5] and the Global Burden of Disease [6,7] have to apply very sophisticated modelling methods to these very scanty data in order to generate outputs that hopefully reflect realities of maternal mortality patterns, with varying degrees of success [8,9]. We characterize these processes here as "top–down".

The alternative approach, for a country or a region, is to undertake direct measurement of maternal mortality, in order to inform health service management and planning, and to provide strategic insights in terms of necessary interventions. We characterize this as a "bottom–up" approach. Despite high top–down MMRs reported for Ethiopia [5,7], no current accurate estimate of the indicator and the underlying causes of avoidable maternal mortality is available on a population basis for the Tigray Region. This is partly due to the difficulties of finding and correctly identifying maternal deaths and ascertaining levels of maternal mortality at the community level. Hence local numbers for maternal deaths tend to only be derived from health facility data, which do not reflect the population–level situation. However, evidence on the magnitude and underlying causes of maternal deaths is essential for planning preventive measures to reduce maternal mortality in the Region. Accurate information on maternal deaths enables tracking progress of feasible health interventions, taking timely actions and increasing the intensity of accountability at all levels – government, civil society organizations, health care providers and donors [1,10-12].

Therefore, the aim of this study was to undertake a bottom–up assessment of maternal mortality for Tigray Region, in northern Ethiopia, identifying overall levels, specific causes and local determinants, and to compare the findings in relation to the various top–down estimates of maternal mortality that are available for Ethiopia.

METHODS

Study settings

Tigray Region is the northernmost of the nine Regional States of Ethiopia and has a total population of more than 5.1 million. The major urban centre is the regional capital,

Mekele, from where health services are coordinated. Rural inhabitants constitute 81.5% of the Region's population, living in an area of 50 078 km^2, with a mean population density of 102 km^{-2}. The maximum distances within the Region are 360 km east–west and 250 km north–south, and altitude above mean sea level varies between 600 m and 3950 m. The Region contains 1 165 575 households (HH), with an average of 4.4 persons per HH (3.4 persons per HH in urban areas and 4.6 persons per HH in rural areas). Health services in the Region are administered in six rural Zones, which are further divided into 34 Districts (locally known as *woreda*), each containing about 25 000 to 30 000 HHs (**Figure 1**). The Region is bordered to the north by Eritrea, to the south by Amhara Regional State, to the east by Afar Regional State and to the west by Sudan. In the Region, there are 15 hospitals, 214 health centres and 604 health posts [14]. Based on the Ethiopia Demographic and Health Survey 2011 (EDHS), conducted from September 2010 to June 2011, antenatal care coverage from a skilled provider was reported for 50.1% of pregnancies, and 11.6% of births were attended by skilled birth attendants, 0.9% by Health Extension Workers (HEWs) and 12.5% by trained Traditional Birth Attendants (TTBA) [14,15].

Study design, sample and sampling procedure

Details of the study design and sampling process for this survey, accompanied by a parallel survey of under–5 deaths, have been described elsewhere [13]. Briefly, sample size estimates for the survey were calculated on the basis that a likely MMR might be 400/100 000 live births, which could be estimated within a 95% confidence interval of 300 to 522 if 54 maternal deaths were observed out of 13 500 live births. Assuming a crude birth rate of 30 per 1000, this would require a population base of 450 000. Since, for op-
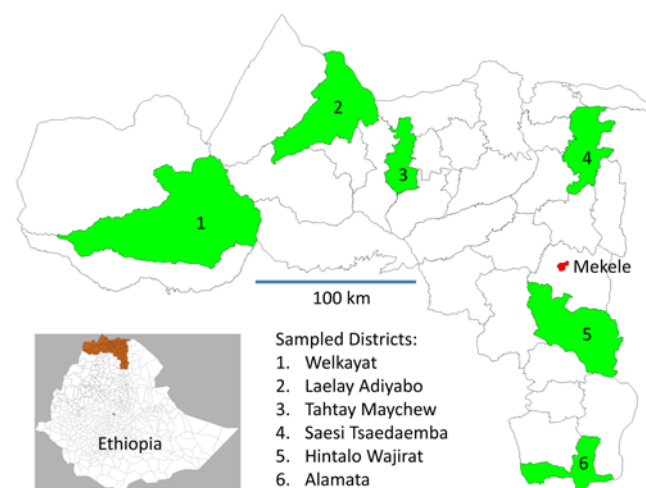
Figure 1. Location of study districts in Tigray regional state, northern Ethiopia (Source: Godefay et al. [13]).

erational reasons, a sample clustered at the District level was required, a design factor of 2 led to target coverage of 900 000, approximately equivalent to six Districts.

The study was conducted in six rural Districts in Tigray region, namely Welkayat, Laelay Adiyabo, Tahtay Maychew, Saesi Tsaedaemba, Hintalo Wajirat and Alamata, which were randomly selected (using the Stata 12 *runiform* function to allocate a random number to every District, then selecting the District with the highest random number from each of the six Zones) as a stratified sample of one District per Zone, as shown in **Figure 1**. The sampled Districts included a total of 183 286 HHs, with a total population of 843 115, covering around 20% of the total population of rural Tigray. Of these, 166 515 were women of reproductive age, defined as 15–49 years, representing 19% of women of reproductive age in rural Tigray.

Data collection procedure

A census of all households was conducted in mid–2013 in the six randomly selected districts to identify all deaths to women of reproductive age that occurred between May 2012 and April 2013, irrespective of the cause, as shown schematically in **Figure 2**. In the same process all live births were identified. For each death identified in the selected districts, a trained health extension worker, responsible for all households in the sub district, visited the household of the deceased women to carry out a VA interview. Respondents were adult relatives who were caregivers at the time of death. The VA questionnaire used was adapted into the local language from the 2012 WHO Verbal Autopsy instru-

Figure 2. Schematic design of pregnancy–related mortality survey in six Districts, Tigray Region.

ment for death of a person aged 15 years and above [16]. Supervisors were trained by the principal investigator for one day and the interviewers were trained by the supervisors for three days on the details of VA tool, interviewing techniques, indigenous terminologies, concepts of illnesses and their manifestations.

Data processing and analysis

The VA data were processed using the InterVA–4 (version 4.02) model, using probabilistic modelling to assign cause of death instead of physicians [17,18]. This resulted in up to three probable causes of death per case, each with an associated likelihood. Cases where there was inadequate detail from the interview material – perhaps because of a lack of direct knowledge by the VA respondent – led to a totally indeterminate outcome, and where details were scanty the three probable causes did not achieve likelihoods summing to 100%. Thus residual likelihoods were assigned to be of indeterminate cause as recommended in the InterVA literature [18]. Consequently the indeterminate proportion of deaths encapsulates the degree of certainty with which cause of death assignments were possible. Finally, all deaths to women of reproductive age that occurred during the target year while pregnant or within 6 weeks of pregnancy ending or abortion, as classified by the InterVA–4 model, were considered as pregnancy related (**Figure 2**). As discussed below, we made the conservative assumption for calculating MMR to consider all pregnancy–related deaths as maternal deaths. The total number of pregnancy–related deaths identified through the VA and the total number of live births identified through the household census were used to compute maternal mortality ratios (MMR) and expressed per 100 000 live births. To calculate 95% confidence intervals around MMR estimates, the Poisson distribution was assumed, using the Stata 12 *cii* command.

Ethics

Ethical approval for the study was granted by the Institutional Review Board (IRB) of the College of Health Sciences of Mekele University, Ethiopia.

RESULTS

A total of 181 deaths among women of reproductive age and 19 179 live births were identified in the six selected Districts within the 12–month study period. Of the 181 deaths, 51 (28%) were ascertained as pregnancy–related deaths. **Table 1** summarizes the characteristics of the women who died of pregnancy related causes. Overall 24/51 (47.1%) of these deaths occurred in Welkayat district. The 25–34–year age group accounted for 23 (45.1%) of the deaths and 49 (96.1%) of the women who died were married or living with a partner. Forty one (80.4%) of the
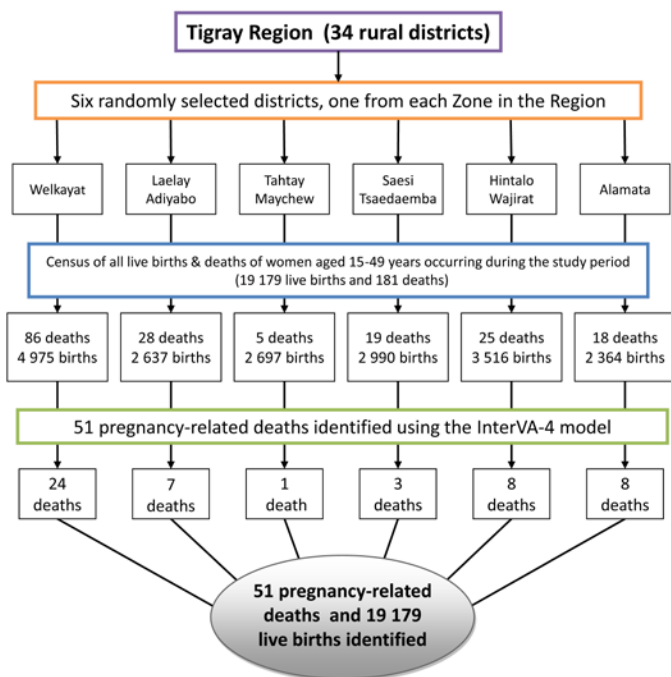
Table 1. Characteristics of 51 women who died during pregnancy or within 42 days of pregnancy ending in 6 sampled Districts, Tigray Region, Ethiopia, from March 2012 to April 2013

CHARACTERISTIC	NUMBER	%	TOTAL POPULATION	HEALTH CENTRES	HEALTH POSTS
Welkayat	24	47.1	171 302	7	25
Laelay Adiyabo	7	13.7	137 296	5	22
Tahtay Maychew	1	2.0	121 355	5	19
Saesi Tsaedaemba	3	5.9	122 479	7	26
Hintalo Wajirat	8	15.7	186 244	7	23
Alamata	8	15.7	104 439	5	15
Age group (years):					
15–24	10	19.6			
25–34	23	45.1			
35–49	18	35.3			
Marital status (at death):					
Never married	2	3.9			
Married or living with a partner	49	96.1			
Education level:					
No formal education	41	80.4			
Started formal education	10	19.6			
Occupation:					
Housewife	36	70.6			
Farmer	9	17.6			
Private employee	4	7.8			
Other	2	3.9			
Place of death:					
Health facility	15	29.4			
Home	36	70.6			
Timing of death:					
Pregnancy ended within 6 weeks of death	28	54.9			
Pregnant at death	23	45.1			
Place of delivery (n = 28):					
Health facility	5	17.9			
Home	23	82.1			
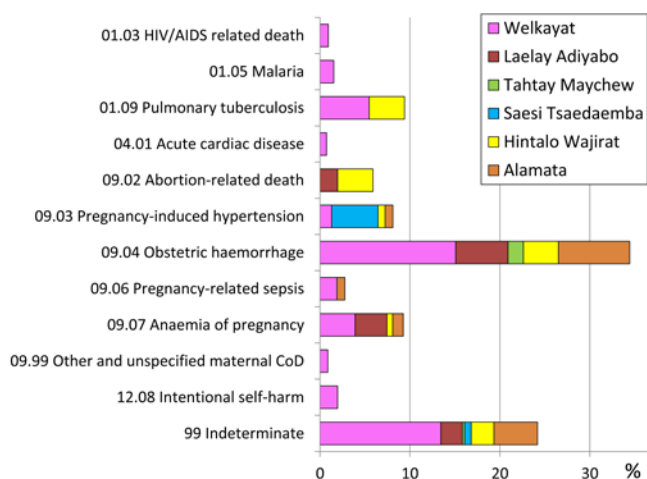
women who died had no formal education. Twenty eight (54.9%) of the deaths occurred after delivery or within six weeks of pregnancy ending and 23 (45.1%) of deaths occurred during pregnancy. Of the 28 women who died after delivery, 23 (82.1%) gave birth at home, while only 5 (17.9%) delivered at a health facility.

Figure 3 shows causes of death in WHO 2012 VA cause of death categories (16) for the 51 pregnancy–related deaths, by District, as determined by the InterVA–4 model. In addition, the commonest causes of indirect causes of maternal death identified were anemia (12%) followed by pulmonary tuberculosis (10%), with both HIV/AIDS and malaria causing 2% of maternal deaths. Out of the 51 pregnancy–related deaths recorded, 61.3% were ascribed to direct obstetric causes. The most common obstetric causes were obstetric haemorrhage (34.4%), followed by anaemia of pregnancy (9.3%) and pregnancy–induced hypertension (8.1%). Post–abortion deaths accounted for 5.9% of pregnancy–related mortality.

Table 2 shows estimates of MMR by District, age group, marital status and education. The magnitude of MMR ranged from 37 deaths per 100 000 live births (95% CI 1–207) in Tahtay Maychew District to 482 deaths per 100 000 live births (95% CI 309–718) in Welkayat District. Thus there were statistically significant variations in MMR within the six Districts surveyed. In view of the substantial variations in MMR between Districts, we looked at possible geographic determinants of these differences, including the populations and surface areas of Districts and distances from the Regional capital, Mekele. We found that MMR was significantly correlated with population density at the District level ($r^2 = 0.86$, $P = 0.005$), as shown in **Figure 4**. MMR did not vary significantly by age group, marital status or education, though the small number of deaths among and

Figure 3. Percentage distribution of 51 pregnancy–related deaths among women aged 15–49 years from March 2012 to April 2013, Tigray Region, Ethiopia, by WHO verbal autopsy cause categories and District.

Figure 4. Correlation between maternal mortality ratios (MMR, per 100 000 live births) and population density (km^{-2}) for six Districts in Tigray Region, Ethiopia ($r^2 = 0.86$, $P = 0.005$).

Table 2. Maternal Mortality Ratios (MMR) per 100 000 live births among rural women aged 15–49 years in Tigray Region, Ethiopia, from March 2012 – April, 2013

Characteristic	Number of pregnancy—related deaths	Number of live births	MMR per 100 000 live births* (95% CI)
District			
Welkayat	24	4975	482 (309–718)
Laelay Adiyabo	7	2637	265 (107–547)
Tahtay Maychew	1	2697	37 (1–207)
Saesi Tsaedaemba	3	2990	100 (21–293)
Hintalo Wajirat	8	3516	228 (98–448)
Alamata	8	2364	338 (146–667)
Age group (years):			
15–24	10	3076	325 (156–598)
25–34	23	9432	244 (155–366)
35–49	18	6668	278 (165–440)
Marital status:			
Never married	2	247	810 (98–2925)
Married or living with a partner	49	18 300	268 (198–354)
Education level:			
No formal education	41	14 979	274 (196–371)
Started formal education	10	4110	243 (117–447)
Overall	**51**	**19 179**	**266 (198–350)**

CI – confidence interval

*Calculated using all pregnancy–related deaths.

Figure 5. Available top–down estimates of maternal mortality ratios (MMR, per 100 000 live births) for Ethiopia made in recent years, together with the results for Tigray Region from this study, 2012–2013. (GBD 2013 [7]; EDHS 2005 [15]; WHO 2008 [3]; EDHS 2011 [15]; GBD 2010 [6]; WHO 2010 [4]; WHO 2013 [5]).
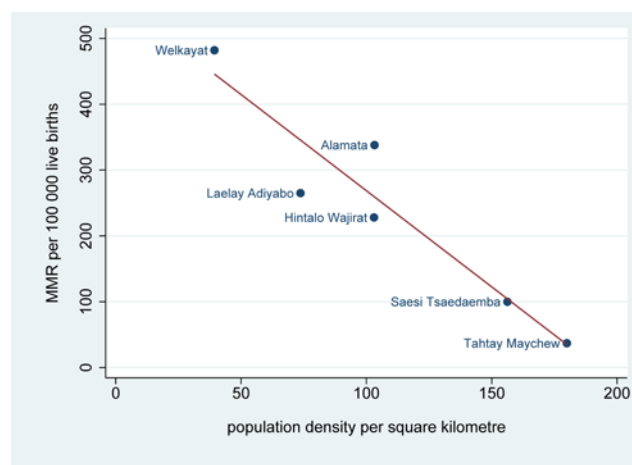
births to unmarried women appeared to carry a higher risk. The overall estimate of MMR across all six Districts was 266 per 100 000 (95% CI 198–350).

In contrast to these bottom–up results, **Figure 5** shows a compilation of available top–down estimates for MMR in Ethiopia in recent years [3-7,15].

DISCUSSION

The major findings from this study were a new assessment of MMR for six districts in the Tigray Region at 266 deaths per 100 000 live births (95% CI 198–350), and an indication of possible wide variations between the sampled Districts. The confidence interval for the six districts' MMR overlaps the uncertainty intervals for the UN national estimates for Ethiopia, which reported 350 deaths per 100 000 live births (uncertainty interval 210–630) for 2010 [4] and 420 (uncertainty interval 240–720) for 2013 [5]. The WHO national MMR estimates for neighbouring countries (Eritrea, Sudan and Djibouti) in 2013 also overlapped with our results from Tigray. Estimates for Ethiopia from the Global Burden of Disease project were generally higher, with smaller uncertainty intervals, than the WHO estimates, for reasons that are not entirely clear [6,7]. All of the global estimates models rely heavily on available data going back to at least 1990 to make their current estimates,

and this tends to mean that the models are not very sensitive to rapid changes in MMR that may occur in recent periods, particularly if there is a lack of corresponding new data at the national level. Because other Regions do not have their own current estimates of MMR, it is impossible to know where these estimates from Tigray would rank in the national picture for Ethiopia.

Findings on MMR in this study were much lower than those from various rounds of the Ethiopian Demographic and Health Survey (EDHS), which reported an MMR of 676 per 100 000 live births (95% CI 541 – 810) for the period 2005–2011 [15], even though DHS uses the same definition of pregnancy–related deaths and MMR. This may be partly due to the EDHS methodology providing estimates for a six year period, and may reflect higher levels of MMR in some other Regions. Unfortunately the EDHS samples are not large enough to break down MMR by Region. Thus it was not possible to see how Tigray as a whole has performed in relation to MDG5.

Tigray Health Bureau has introduced a number of innovations targeted at reducing maternal mortality in recent years. These include leadership commitment and innovative approaches to supporting organized community mobilization for health. A woman–centred "one to five network" encourages every woman of reproductive age to engage voluntarily with small, local groups of neighbouring women (with 30 households on average being organized into a "Women's Development Team"). Health facilities are being made more friendly to community members, preparing pregnant mothers for skilled delivery and post–natal care through monthly meetings, establishment of maternity waiting rooms, and offering traditional Ethiopian

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coffee ceremonies at delivery facilities. There is substantially increasing coverage of four–wheel drive ambulance services in every District, as well as "traditional ambulances" (locally made stretchers for carrying women in labour to health institutions in remote places). Additionally, one or two midwives trained in basic emergency management of neonatal care (BEMONC) have been assigned for every 25 000 population and basic emergency obstetric services like emergency surgery units placed in primary hospitals (designed to provide comprehensive preventive and curative service for every 100 000 population) are substantially more accessible than previously [19].

Our study showed that the majority of pregnancy–related deaths (36, 70.6%) occurred at home. This finding is comparable with studies conducted in India [20] and other low and middle income countries [21]. There may be many reasons for that, but it highlights the challenge to not only provide emergency obstetric services in an environment like Tigray, but also to get women in urgent need of care to facilities. Direct obstetric causes accounted for the majority (61.3%) of pregnancy–related deaths. The main direct and indirect causes were haemorrhage (34.4%), anaemia of pregnancy (9.3%) and pregnancy–induced hypertension (8.1%). These are all causes which can be reduced by effective emergency antenatal care and skilled care at birth to prevent, detect and manage mild complications, and obstetric care. However, our results were consistent with other studies, for example in Sokoto, Western Nigeria [22] which reported 48.3% of maternal deaths due to postpartum haemorrhage and a previous study from Tigray that reported 39% of maternal deaths due to haemorrhage [23]. Pregnancy–induced hypertension has also been reported as a major cause of maternal death in other studies, for example 19% in Nigeria [22], 28% in Haiti [24] and 19% in Tigray [11]. This might reflect a lack of access to anticonvulsant drugs like magnesium sulphate, either because of stock issues or lack of appropriate use, assuming that women get to facilities in the first place.

Indirect causes of maternal mortality are difficult to account for using verbal autopsy methods because of the need to make a judgment about the extent to which final illnesses might be ascribed to pregnancy. Garenne and colleagues have discussed the relevance of the concept of indirect maternal mortality, particularly in relation to the impact of HIV infection on pregnancy–related mortality [25]. Consequently, in this study we have taken the conservative approach of including all pregnancy–related deaths in estimates of MMR, even if that results in higher estimates of maternal deaths. This also avoids the difficulty of how to assign pregnancy–related deaths of indeterminate cause to maternal deaths, which is a problem that inevitably arises where VA respondents do not have sufficient knowledge of the case details.

The wide variations in MMR across the six Districts surveyed were somewhat surprising. Some of this variation might be accounted for by factors such as remoteness of some Districts, with hard–to–reach and scattered populations, which in turn might lead to limited access to health services, transport and other infrastructure. In Welkayat District, which recorded the highest MMR, five sub–districts (locally known as *kebeles*) did not have Health Extension Workers in place. The high turnover of health workers due to difficult living environments and less participation by development partners such as non–governmental organizations and faith–based organizations may lead to higher MMRs in remote areas. Maternal deaths were reported to be clustered in one district in another study conducted in Artibonite, rural Haiti [24]. Because of the extent of variation between Districts in our study, we looked for geographical factors that might help to understand the causes. We found a strikingly strong correlation between population density and MMR (**Figure 4**). The reasons for this are not immediately clear, but, since various levels of health services are normally provided on a per–population basis, rather than by size of geographical area, it is likely that access to health care is more challenging in Districts with lower population densities. This in turn suggests that logistic constraints probably persist as a major determinant of maternal mortality.

Possible limitations of our study include potential recall bias in identifying pregnancy–related deaths up to a year after they occurred, which would not happen if real–time death registration were in place. Nevertheless the recall demands over a one–year period are substantially less than those required in the EDHS methodology. However, pregnancy–related deaths are generally considered to be important and therefore memorable events within households, and it has been demonstrated that VAs can be administered reliably even after relatively long recall periods [26]. There is a further potential problem arising from the possibility of a household dissolving after the death of the mother as a key member, and consequently not being included in a retrospective survey. This probably occurs relatively rarely in the typical extended family structures in rural Ethiopia. Unlike some surveys of maternal mortality, we avoided the bias that can arise by identifying maternal deaths before determining cause of death, since we followed up all identified deaths among women of reproductive age.

In a one–off survey of this kind, it is not possible to assess the dynamics of MMR. However, by chance, one of the Districts surveyed here, Alamata, was also surveyed using a very similar methodology as part of a malaria treatment investigation in 2005–7 [27]. Live births were not counted in that survey, but 23 obstetric deaths were recorded over that two–year period in the Alamata District, compared with 5 obstetric deaths over a one–year period in this study.

CONCLUSIONS

Our success in arriving at a bottom–up contemporary estimate of MMR for a sample of Tigray Region, as a result of undertaking a relatively straightforward population survey, is encouraging. At the same time, we were able to gain insights on apparently wide inter–District variations which are potentially important for planning maternal health services in the Region. Our experience suggests that it may be quite feasible for regions within larger sub–Saharan African countries, or for smaller countries at national level, to undertake similar surveys of local MMR, and we suggest that this approach should also be used more widely to monitor, supplement and strengthen maternal death surveillance and response (MDSR). The correlation we found between MMR and population density suggests that logistic factors remain a major determinant of maternal mortality in Tigray. The majority of pregnancy–related deaths, as determined using the WHO 2012 and InterVA–4 verbal autopsy tools arose from potentially preventable causes. This highlights the need to provide preventive and emergency obstetric care that is not only clinically effective but also accessible. The use of community mass media to increase the awareness of mothers about the advantages of skilled delivery services and involvement of male decision–makers regarding maternal health services also need to be given priority. Additionally, providing better incentives for health workers to stay in the more remote areas, and enhancing the ambulance system in those areas, should ensure a better and more sustained service.

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Effect of community mobilization on appropriate care seeking for pneumonia in Haripur, Pakistan

Salim Sadruddin[1], Ibad ul Haque Khan[2], Abdul Bari[3], Attaullah Khan[4], Ijaz Ahmad[5], Shamim A. Qazi[6]

[1] Save the Children US, Fairfield, CT, USA

[2] Save the Children, Pakistan Program, Islamabad, Pakistan

[3] Independent consultant, formerly with Save the Children, Pakistan

[4] Directorate General Health Services, Peshawar, Khyber Pakhtunkhwa, Pakistan

[5] Health Sector Reform Unit, Department of Health, Peshawar, Khyber Pakhtunkhwa, Pakistan

[6] World Health Organization, Department of Maternal, Newborn, Child and Adolescent Health, Geneva, Switzerlandi

Correspondence to:

Dr Salim Sadruddin
Save the Children
501 Kings Highway East, Suite 400
Fairfield CT 06825
USA
ssadruddin@savechildren.org

Background Appropriate and timely care seeking reduces mortality for childhood illnesses including pneumonia. Despite over 90 000 Lady Health Workers (LHWs) deployed in Pakistan, whose tasks included management of pneumonia, only 16% of care takers sought care from them for respiratory infections. As part of a community case management trial for childhood pneumonia, community mobilization interventions were implemented to improve care seeking from LHWs in Haripur district, Pakistan. The objective of the study was to increase the number of children receiving treatment for pneumonia and severe pneumonia by Lady Health Workers (LHWs) through community mobilization approaches for prompt recognition and care seeking in 2 to 59 month–old children.

Methods To assess pneumonia care seeking practices, pre and post–intervention household surveys were conducted in 28 target Union Councils. Formative research to improve existing LHW training materials, job aids and other materials was carried out. Advocacy events were organized, LHWs and male health promoters were trained in community mobilization, non–functional women and male health committees were revitalized and LHWs and male health promoters conducted community awareness sessions.

Results The community mobilization interventions were implemented from April 2008 – December 2009. Project and LHW program staff organized 113 sensitization meetings for opinion leaders, which were attended by 2262 males and 3288 females. The 511 trained LHWs organized 6132 community awareness sessions attended by 50 056 women and 511 male promoters conducted 523 sessions attended by 7845 males. In one year period, the number of LHWs treating pneumonia increased from 11 in April 2008 to 505 in March 2009. The care seeking from LHWs for suspected pneumonia increased from 0.7% in pre–intervention survey to 49.2% in post–intervention survey.

Conclusion The increase in care seeking from LHWs benefited the community through bringing inexpensive appropriate care closer to home and reducing burden on overstretched health facilities. The community mobilization interventions led to improvements in appropriate care seeking that would not have been achievable just by strengthening pneumonia case management skills of LHWs. In addition to strengthening skills, community mobilization and behavior change activities should also be included in community case management programmes.

Over 120 million pneumonia cases occur annually resulting in an estimated one million deaths in children under five years of age [1–3]. Over 80% pneumonia deaths occur at home [4]. Pakistan is among the top five countries that contribute to majority of these pneumonia episodes and deaths globally [5].

In children, a non–fatal disease can progress within 2–3 days to a fatal outcome if appropriate care is not provided in time [6–9]. Where access to health care is low, WHO and UNICEF recommend that trained community health workers (CHWs) treat pneumonia with oral antibiotics [10]. This requires deployment of trained CHW in the community, household recognition of pneumonia and prompt care seeking. Interventions promoting care seeking improve mortality outcomes, but timely care seeking from an appropriate care provider is essential [11,12].

Recognition of a pneumonia episode by the care takers is low in developing countries including Pakistan [13]. Sometimes, they may recognize the symptoms, but delay care seeking [14]. Appropriate care seeking from health workers trained in standard pneumonia case management is low, particularly in rural and poorer communities [5]. A systematic review of studies from developing countries, including Pakistan found that care seeking from available CHWs for pneumonia was only 4.2% [13].

There may be concern about antibiotic misuse by CHWs in the community for treatment of pneumonia. However, it has been shown that trained CHWs using standard case management of pneumonia can reduce both pneumonia specific and infant mortality [15,16]. Moreover, standard case management of pneumonia at facility and community level improves rational use by reducing inappropriate antibiotic usage [17–20], potentially resulting in less pressure on antimicrobial resistance. However, in Asian countries majority of care seeking for suspected pneumonia is from private providers and one of the reasons for seeking care from private providers is the increased likelihood of receiving injections for pneumonia and antibiotics for diarrhoea, which is perceived to be an appropriate treatment [13]. Irrational drug use by general physicians and occasionally by pediatricians has been reported from Pakistan as well [21–23].

To extend health services to the community and household level, Government of Pakistan launched the National Programme for Family Planning and Primary Health Care, hereafter called Lady Health Worker (LHW) Programme in 1994. This community based literate woman trained as health worker is known as LHW. She provides health education, family planning and curative care for childhood illnesses including pneumonia. By 2007, over 90 000 LHWs were trained and deployed in rural and semi–urban areas,

covering 60% of the population [24]. An independent program evaluation showed that care seeking for children with respiratory infection from LHWs was reportedly only 16% [21].Most families believed such consultation from LHW was unnecessary. The national LHW Programme (LHWP) and Save the Children with technical support from WHO implemented a community mobilization program to improve appropriate care seeking for pneumonia in children in Haripur district, Pakistan. It was part of a cluster randomized clinical trial for treatment of pneumonia for children under five years of age, which has been reported elsewhere [25].

METHODS

Study design and objective

This was a cross-sectional study with pre and post intervention assessments for pneumonia care seeking coverage. The objective of the study was to increase the number of children receiving treatment for suspected pneumonia by LHWs through community mobilization approaches for prompt recognition and care seeking in 2 to 59 month–old children.

The primary outcome was the proportionate change in care–seeking from LHWs by caretakers for suspected pneumonia among children 2–59 month-olds. Appropriate care seeking defined as standard case management of pneumonia – National Integrated Management of Childhood Illness guidelines for facility providers and Community Case Management (iCCM) guidelines for community health workers.

Study setting

Haripur district located in Khyber Pakhtunkhwa Province (KP) is administratively organized into two sub–districts (Tehsils) and 44 Union Councils (UC), the smallest administrative unit with a population of 15–25 thousand. In 2008, the projected district population was approximately 856 000, with eighty eight percent living in rural areas [26]. The care seeking interventions were implemented in 28 union councils.

The public sector health infrastructure in Haripur district has one district hospital, five rural health centers (RHCs), 41 basic health units (BHU), 14 other health centers and 750 LHWs. The private sector has seven general hospitals, three maternity homes and several clinics. In addition, local pharmacists and chemists also provide curative care to the community. Each UC has one BHU or an RHC.

LHWs provide preventive and promotive care to children and mothers, and basic curative services for children. LHWs have at least an eighth grade education and receive

three months classroom training followed by 12 months of field practice under supervision. LHWs work from health houses established at their residence and serve around 1000 individuals (150–200 families). They conduct five to eight household visits per day, visit each household at least once a month and are available for sick child visits at their health house or the child's residence. They are linked to the nearest public sector Basic Health Unit (BHU)/Rural Health Center (RHC) for clinical supervision, replenishment of supplies, and in–service training. The LHW is supervised by a lady health supervisor (LHS). Each LHS supervises 15–20 LHWs and visits each LHW at least once a month. The LHS is provided a vehicle, driver and fuel by the LHW programme for field supervision.

The local government structure at district level at the time of the study consisted of elected Nazim (Mayor) who headed the district assembly, which comprised of elected councilors from UCs. Since January 2010, the local government system at the district level is in abeyance and an ad hoc system of administration has been put in place.

Study interventions

Two community mobilization strategies were implemented in the 28 union councils. The main purpose was to create awareness on signs/symptoms of pneumonia, importance of early care seeking, and the role of LHWs in treatment of pneumonia.

1. District and union council level sensitization

Individual and group meetings at district, tehsil and union council levels with district, tehsil and UC Nazims, religious leaders, teachers and male and female councilors were conducted. Senior staff from the project and LHWP conducted group and one to one meetings. The discussions focused on pneumonia burden, signs of pneumonia, importance of early recognition of pneumonia at household level and prompt treatment at community level and the project objective to strengthen LHW capacity to educate families to recognize signs and symptoms; diagnose and treat pneumonia; and refer cases to appropriate health facility, where needed. Formative research findings showed that the main reason for low care seeking from LHWs was community perception that LHWs provide only health education to mothers and children, with limited or no role in treatment of illness. During the meetings clear messages around LHWs' capacity to manage pneumonia and the additional training she received was emphasized. Support from community leaders was sought for disseminating messages to their respective communities, and motivate households to seek care from the LHW. Individual meetings were followed by formal presentations at district and UC assemblies and UC level sensitization meetings for male and female councilors. In turn, the opinion leaders spoke about the initia-

tive in the relevant forums and their regular interaction with community members. The District Health Board (DHB) headed by the district Nazim was actively engaged and updates on project activities were provided during the DHB quarterly meetings.

2. Community level sensitization

Training of lady health workers, male promoters and development of job aids. According to LHWP guidelines, in each LHW catchment area, women and male health committees were to be established to engage the community in LHWs' activities and to create awareness. It required each LHW to conduct one community session per month on maternal and child health issues in her catchment area. However, the pre service training did not prepare her well enough to engage with women in the community. In most cases either the committees were nonexistent or non–functional. As part of this project women and men health committees were reactivated or established, where absent.

As LHWs' access to male community members was low due to cultural barriers, we requested communities to nominate a male volunteer as health promoter from LHW catchment area to facilitate her work and to conduct community awareness sessions for male community members. The LHW and the male promoter from LHW catchment area were trained to strengthen their skills for community engagement and facilitating community sessions. The training included classroom sessions, role plays and supervised community session. Initial two day training was followed by regular on site mentoring by the LHS and six monthly refreshers. Based on the qualitative research findings, pictorial counseling cards with culturally appropriate messages on signs of pneumonia and appropriate treatment, sources of care and home care for the treated child were developed. The LHWs and male promoters were trained to use the materials to give simple and clear messages to the community. In all 511 LHWs and 511 male health promoters from 28 UCs were trained.

Community sessions. After the training LHWs and male health promoters started conducting community awareness sessions (CAS) for female and male community members respectively. Each LHW conducted at least one CAS monthly attended by 8–15 mothers and elder women in the community. Care takers, whose children had been treated by the LHWs also attended the sessions and shared their experiences with other women. These sessions helped create awareness on pneumonia signs, timely and appropriate care seeking from LHWs in their communities. Another objective was for the session participants to share the messages and experiences with their kin and neighbors. The sessions were periodically monitored by the LHS for quality purposes. Also, during her daily visits to 5–7 households, LHW counseled mothers and other female caretak-

ers using counseling charts with pictorial messages. The male activist conducted scheduled periodic sessions and also when requested by the LHW. The methodology and content was same as in the LHW sessions. Fathers whose children had been treated by the LHWs also attended the sessions as advocates for care seeking from LHWs. Examples of community experience are given in **Box 1**.

Data collection

Household surveys. To assess baseline knowledge of care–takers on suspected pneumonia, household and care–seeking practices, and sources of care, a pre–intervention household survey was conducted [27]. Using the formula for sample size for comparison of two proportions for cluster randomized trials [28] and assuming 15% refusals and persons not contactable during the survey we needed to interview a total of 6160 households – 220 households each in the 28 union councils (UC). This would allow us to detect a 20% absolute increase in the proportion of children with suspected pneumonia for whom care was sought from a provider.

A two stage sampling strategy was used. At the first stage four villages were selected at random from each of the 28 UCs. At second stage a fixed sample of 220 households were proportionately distributed among the four selected villages in each UC. One hundred and eighty five HHs were additionally included in the sample for anticipated refusals.

We used a structured questionnaire, adapted from a validated set of 2006 Pakistan Demographic and Health Survey questionnaire. In the sampled household a respondent above the age of 18 was interviewed to determine if a child under five years of age had respiratory symptoms in the two weeks preceding the survey. If a child was identified as having respiratory symptom, the caretaker of the child was asked whether or not they had sought treatment and the source of treatment, if any. The standard DHS definition was used to define "suspected pneumonia", ie, cough with or without fever and difficulty breathing that was due to a problem in the chest.

Using the same baseline survey methodology and data collection tools a post–intervention survey was conducted to assess the impact of community interventions [29].

Data on number of LHWs treating pneumonia is from the community case management of severe pneumonia cluster randomized trial [25].

Data analysis

Household survey date was double entered in CSPro software (US Census Bureau) and analyzed in SPSS version 15 (IBM SPSS Statistics).

Formative research

A qualitative study was conducted in September 2007 to inform the results of the quantitative survey and to assess: the current knowledge of mothers and LHWs about child-hood pneumonia; the terminologies commonly used for different signs/symptoms of pneumonia; the home management and care–seeking practices outside home; care taker attitude towards LHWs and other services and use of antibiotics and harmful drugs and; factors that limited care seeking from outside home. Focus Group Discussions were conducted with mothers of children under five years of age in five different Union Councils. Findings were used to improve existing LHW training manual and develop information education and communication (IEC) materials for use during advocacy events and community awareness sessions.

RESULTS

For sensitizing communities and improving care seeking, senior project and LHW program staff organized 40 male and 73 female meetings for district council members, local councilors, religious leaders, teachers and other opinion leaders from the 28 union councils during the project period. Over a 20–month period a total of 2262 males and 3288 female community members attended the meetings.

The 511 LHWs from the 28 union councils initiated community mobilization activities and started case management of pneumonia as part of project activities [22]. The LHWs organized 6132 community awareness sessions with 50056 women attending these sessions. Similarly, male promoters conducted 523 sessions with 7845 males attending these sessions. In addition to the direct effect, secondary diffusion occurred through men and women attending the sessions.

The pre–intervention survey was conducted in April–May 2007 and the post intervention survey in April–May 2010. Respondents from 6224 and 6345 households were interviewed in the pre–intervention and post–intervention surveys respectively. The households were similar in terms of ethnicity, educational level of the head of the households, and home ownership.

In pre–intervention survey, care takers of 80.8 of children under five years of age with signs of respiratory illness in the last two weeks reported seeking care for the child's illness. Majority (36.1%) of the care takers sought care from private clinics followed by public sector referral facilities (23.1%) and private hospital (14.5%) (**Figure 1**). Only 2.4% sought care from Basic Health Units and 0.7% from the LHWs [24]. The main reason cited for not seeking care from the LHWs was lack of knowledge about their ability to treat pneumonia.

In the post–intervention survey, the overall care seeking for children with cough and difficult or fast breathing in the last two weeks increased to 95.6% [26]. Besides increase in overall care seeking, substantial changes occurred in care

PRE-INTERVENTION

POST-INTERVENTION

Figure 1. Sources of care seeking for children under five years of age with suspected pneumonia from pre and post intervention household surveys.

Figure 2. Lady Health Workers (LHWs) who reported treating childhood pneumonia after initiation of project activities in April 2008.

DISCUSSION

Our results show that community mobilization interventions led to an overall increase in care seeking for pneumonia, particularly from LHWs, which increased from 0.7% to 49.2% in three years. Additionally, the number of LHWs treating pneumonia cases went up from 11 to 505 in twelve months. In the 28 union councils of District Hairpur, LHWs treated 45% of all expected cases of pneumonia.

The increase in care seeking from LHWs resulted in a shift in care seeking from private clinics and hospitals and other referral facilities. Other studies have also observed the effect of community interventions to create awareness on behavior change. An Indian study looking at improving prevention and treatment of malaria through community mobilization also found shift in care seeking to community health workers and increase in prompt diagnosis and treatment [31]. A study implementing programme to create care taker awareness about danger signs through group and one to one health education sessions in peri–urban areas of Lusaka, Zambia increased care seeking for children with danger signs from 56% at baseline to 65.8% at follow–up three years later [32,33]. The study found that educating caretakers on danger signs and need for prompt action through appropriate interventions can change behaviors, overcome distance and cost barriers, and increase care seeking. The shift in care seeking from health facilities to LHWs benefited the community by bringing free and quality care closer to home resulting in reduced burden on the families in terms of costs for travel and treatment [34]. Furthermore, it diminished burden on the already over-stretched public sector facilities. The companion treatment trial found that children referred for treatment of pneumonia received non–standard treatment in the shape of multi–drug therapy [22]. This is similar to the inappropriate prescribing practices reported elsewhere from Pakistan [19,20].

seeking patterns. The majority (49.2%%) of care takers sought care from the LHWs, followed by private clinics (15.7%), private hospital (9.0%), and public sector referral facilities (8.9%). The number of children seeking care from BHUs also increased (5.7%).

Besides increase in care seeking for pneumonia from LHWs, in one year period the number of LHWs treating children with pneumonia increased from 11 in April 2008 to 505 in March 2009 (**Figure 2**).

We also calculated the proportion of expected cases treated by the LHWs for the April 2008–March 2009 twelve month period. Using estimated incidence of 0.41 episodes per child/y for Pakistan [30] we calculated that of the 31 462 (0.41×76735) expected cases of pneumonia in children under five years of age in the 28 union councils, LHWs managed 14 057 cases, ie, 45% of the cases. This validates the post–intervention care seeking figure of 49.2%% from LHWs.

It is reported that although the deployment of CHWs brings care closer to the community, it does not always lead to increased utilization [35]. The main reason cited for not seeking care from the CHWs was that families did not know that they existed. This confirms our baseline findings that although the LHWs were working in the community for several years the community was not aware of their ability to treat pneumonia [24]. A community based qualitative study in rural Uganda [36] reported that awareness regarding key pneumonia symptoms and use of antibiotics to treat pneumonia was very low. These findings show that only training, equipping and deploying health providers will not result in appropriate and timely care seeking. A level of trust between the CHW and the community is needed to enable relationships that will produce positive health outcomes [37]. The training of LHWs, provision of supplies and their frequent interaction with communities through CAS has helped create this trust for enhanced care seeking from LHWs by the mothers.

LHW and health promoter training to conduct community awareness sessions using culturally appropriate messages and pictorial health education material helped increase awareness, thus improving care seeking. In addition to the direct effect, we believe secondary diffusion occurred through men and women attending the sessions. Parents of children treated by LHWs proved to be strong advocates. Individual advocacy efforts with elected representatives from District to Union council level, teachers, religious leaders, organization of sensitization meetings at local levels and participation and highlighting the issue of pneumonia in District Health Board also played a substantial role in highlighting LHW role in treatment of pneumonia.

A major strength of the study was the Ministry of Health–Save the Children Public–Private partnership and implementation of the project interventions within the existing LHWP structure. LHWs are mandated to carry out community mobilization activities including conducting education sessions on health promotion, prevention and prompt treatment, where necessary. We mainly streamlined and strengthened this component. Minimal additional inputs were provided during the study in the form of training for sensitization and conducting community awareness sessions and monitoring. Second was the involvement of public representatives and other major stakeholders at district and community level at all stages of programme implementation. They became a major resource for information dissemination and problem solving. Finally, the project overcame resistance encountered from physicians and other local health providers as they feared loss of income with LHWs treating pneumonia cases at community level. We conducted sensitization seminars with local health providers and physicians to explain the project objectives and their cooperation was sought to provide referral support.

A general limitation of the before–after design is the change over time influenced by rapidly improving sources of information for improving knowledge and practices and introduction of interventions by other groups. As CAS were carried out across the board in all 28 UCs with no control group, it is possible that other factors may have played a role in improving care seeking. However, we believe that other factors can be eliminated as contributors to change in care seeking for two main reasons; first, to our knowledge there were no campaigns on print or electronic media or by other organizations to disseminate information on pneumonia prevention and care seeking during the study implementation period to which the community may have been exposed; second, we have been working with the public and private sector in the district for over a decade and know that there were no interventions directed towards LHWs or the community to improve care seeking or service delivery at LHW level. The household survey findings of increased care seeking from LHWs are also validated by the routine LHW program service delivery data. Another limitation of our study was the DHS definition for suspected pneumonia. This is not a robust measure and may have overestimated the two–week prevalence of suspected pneumonia. In addition, despite clear definition for sources of care, care takers may have not correctly reported the sources of care. As our sample size was large and the same set of questionnaires and training methodology was used for both pre–intervention and post–intervention surveys, it would not have affected the results for the two time periods.

CONCLUSION

The study findings show that it is possible to mobilize communities to improve appropriate care seeking practices at scale within the public sector. The experience showed that while some extra support was provided to increase community mobilization and retrain LHWs, some of the other key elements such as health committees, LHWs and LHSs already existed in the programme. We also showed that it is important to target both direct community awareness activities at village level, and involve stakeholders at district and sub–district level. Applying the lessons learned from the study in other districts of Pakistan will not require additional inputs in terms of money and human resources. However, to sustain momentum of community mobilization interventions in district Haripur and replication in other districts, it is important that senior provincial and district program managers realize the significance and effectiveness of community engagement interventions and ensure its inclusion in annual work plans and budgets.

The study findings have major implications for Pakistan's LHW programme, where on an average only 16% of children with ARI utilize LHW services for case management [23]. As only a few countries have such a large scale community based programme, the LHW programme provides a huge opportunity for improving access to remote communities and accelerating mortality reduction through standard case management.

Box 1. Community experience

Case 1: Union Council Ali Khan, Village Kaal, District Haripur

Abdul Mannan, Naib Nazim (Deputy Mayor), UC Ali Khan, Haripur, never considered LHW as a health care provider. He thought that LHWs were deployed to provide health education to community women and didn't know that they could treat pneumonia with oral antibiotics. During one of the Union Council sensitization meetings, the project staff briefed Abdul Mannan and other council members on the pneumonia project. However, he was reluctant to accept that LHW was skilled enough to treat pneumonia.

In January 2009, his 10 month–old son Abdul Samad became ill with cough and fever. As Abdul Mannan was out of town his wife called him by telephone to inform him about the son's condition. He enquired about the signs and symptoms of his child's illness. He remembered the information from the sensitization meeting and asked his wife to consult the village LHW. The LHW was called and promptly arrived at their residence. She assessed the child and ascertained that he had pneumonia and gave oral amoxicillin as per standard protocol. The child's condition started improving after receiving four doses of antibiotic and he was symptom free after completing the full course of treatment. Abdul Mannan has now become a strong advocate for LHWs.

Case 2: Union Council Mirpur, Village Rara, District Haripur

Aliya lived in a village 15 km from Haripur town. She has two children and her husband is a day laborer. When Aliya's son developed cough and rapid breathing she became worried as nobody was at home to take the child to a doctor. Aliya had heard about the LHW but thought it would be waste of time to seek care from her as she believed the proper treatment was injections. She consulted her sister–in–law who lived nearby, who told her that the LHW based in the village had treated many cases of pneumonia, and all of them have recovered completely.

Aliya called the LHW, who examined the child and diagnosed pneumonia and gave oral amoxicillin. The child recovered and she was very happy with the timely availability of quality treatment at her doorstep. Now LHW has become her first point of contact for all child related health problems.

The child's grandmother said later "*With the efforts of the LHW the life of our child was saved. We gained knowledge from the LHW about the care of a child and now we can educate other people. We have learned many tips on how to prevent our kids from pneumonia. We can now identify it and know what to do in case the child has pneumonia. We have treatment facility at our door step.*"

We have shown that communities are willing to seek care for quality services, even if they are provided by CHWs. Other large scale community case management programmes in Asia and Africa can benefit from the strategies implemented in Haripur district. Finally, governments and donors making huge investments in infrastructure, capacity building, and medicines have to be cognizant that these inputs are not sufficient to improve treatment services. The experience of LHWP underscores this point. Since its launch 20 years ago and despite having reasonable financial and human resources, it has remained underutilized in the delivery of curative care services. We recommend that in addition to strengthening CHW skills in service delivery, community mobilization and behavior change activities should be integral part of such programmes.

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Barriers and facilitators to the quality use of essential medicines for maternal health in low–resource countries: An Ishikawa framework

Dan N. Tran[1,3], Lisa A. Bero[1,2,3,4]

[1] Department of Clinical Pharmacy, University of California, San Francisco School of Pharmacy, CA, USA

[2] Institute for Health Policy Studies, University of California, San Francisco, CA, USA

[3] World Health Organization Collaborating Centre on Pharmaceutical Research and Science Policy, University of California, San Francisco, CA, USA

[4] Charles Perkins Centre, Faculty of Pharmacy, University of Sydney, Sydney, Australia

Background An estimated 800 women die every day due to complications related to pregnancy or childbirth. Complications such as postpartum haemorrhage (PPH) and pre-eclampsia and eclampsia can be prevented by the appropriate use of essential medicines. The objective of this study was to identify the common barriers and facilitators to the availability and use of oxytocin, ergometrine, and magnesium sulfate ($MgSO_4$) – essential medicines indicated for the prevention and treatment of PPH and pre–eclampsia and eclampsia.

Methods We analyzed seven UNFPA/WHO reports published in 2008–2010. These reports summarized country–wide rapid assessments of access to and use of essential medicines for maternal health in Mongolia, Nepal, Laos, the Democratic People's Republic of Korea (DPRK), the Philippines, Vanuatu, and the Solomon Islands. We used a "fishbone" (Ishikawa) diagram as the analytic framework to identify facilitators and barriers at four health–system levels: government/regulatory, pharmaceutical supply, health facility, and health professional.

Results Common facilitators to the quality use of essential medicines for maternal health were observed at the government/regulatory and health professional level. A majority of countries had these medicines listed in their essential medicines lists. Awareness of the medicines was generally high among health professionals. Common barriers were identified at all health–system levels. First, standard treatment guidelines were not available, updated, or standardized. Second, there was an inadequate capacity to forecast and procure medicines. Third, a required $MgSO_4$ antidote was often not available and the storage conditions for oxytocin were deficient.

Conclusions The "fishbone" Ishikawa diagram is a useful tool for describing the findings of rapid assessments of quality use of essential medicines for maternal health across countries. The facilitators and barriers identified should guide the development of tailored intervention programs to improve and expand the use of these life–saving medicines.

Correspondence to:

Lisa A. Bero, Ph.D.
Chair of Medicines Use and Health Outcomes
Faculty of Pharmacy and Charles Perkins Centre
The University of Sydney
D17, The Hub, 6th floor, Charles Perkins Centre
Sydney, NSW | 2006, Australia
lisa.bero@sydney.edu.au

Approximately 800 women die every day due to complications during pregnancy or childbirth [1]. An overwhelming 99% of these maternal deaths occur in low–resource settings, with Sub–Saharan Africa and Southern Asia accounting for 86% of overall global maternal mortality cases in 2013 [1,2]. Moreover, the probability that a 15–year–old woman will eventually die from a cause related to maternal health is much higher for women living in low income countries than for those who live in high income countries (1:160 vs 1:3700) [2,3]. The higher number of pregnancies on average and a higher risk associated with each birth contribute to the higher adult lifetime risk of maternal death [3].

In 2000, 189 member states of the United Nations adopted eight Millennium Development Goals (MDG) [4]. The fifth MDG aims to reduce maternal mortality worldwide by 75% between 1990 and 2015 [4,5]. Despite a 45% decrease in maternal mortality in the past two decades, the annual rate of decline has been far below the MDG 5 target [2,5,6]. A lack of sufficient antenatal care during pregnancy and inadequate assistance from skilled health providers during delivery contribute to the high maternal mortality rate in developing countries [7]. The World Health Organization (WHO) reports that between 2003 and 2009, more than half of all maternal deaths resulted from haemorrhage (with postpartum haemorrhage (PPH) accounting for more than two thirds of cases), hypertensive disorders (pre–eclampsia and eclampsia), sepsis, and unsafe abortion [8]. WHO has provided evidence–based recommendations for the essential interventions and medicines needed to improve maternal health and prevent these maternal complications [9–12]. Even though the availability of essential medicines for maternal health is not well documented in many countries [13], recent data suggested that it is low in Africa and Asia [14].

To investigate the availability and use of WHO–recommended life–saving medicines for women and children, WHO and the United Nations Population Fund (UNFPA) conducted a descriptive study of essential medications for maternal, child, and reproductive health in seven low–resource countries between 2008 to 2010. The two objectives of our study were: (1) to obtain a "snapshot" of the availability of oxytocin, ergometrine, and magnesium sulfate (MgSO$_4$), and (2) to use the Ishikawa "fishbone" diagram as a framework to describe the common barriers and facilitators contributing to use of these essential medicines.

METHODS

Our primary data sources were the published UNFPA/WHO reports of field assessments conducted in seven countries between September 2008 and November 2010

(available from the authors). The reports summarized country–wide rapid assessments of access to and use of essential medicines for maternal and newborn health care and reproductive health.

Selection of study sites

Seven low–resource countries located in Asia and the Pacific Ocean were included in the study: Mongolia, Nepal, Laos, DPRK, the Philippines, Vanuatu, and the Solomon Islands. In each country, health care facilities (i.e nurse aid posts, health units/centers/clinics, hospitals) and medicine–supply facilities (ie, medical warehouse and pharmacies) from multiple sectors were purposively selected based on the site's population density, site's performance on MDG 5, transportation feasibility, human capacity, and time constraints. The sample included facilities that provided various levels of care (primary, secondary, and tertiary), from different governmental sectors (central, provincial, district, and below), and with different types of financial support (publicly–, privately–, or non–governmental organization–funded).

Selection of medicines

The medicines evaluated were on the WHO Model List of Essential Medicines and some were listed as priority life–saving medicines for women and children by the WHO Department of Essential Medicines and Health Products [11,12]. These medicines included: oxytocin and ergometrine injections for prevention and treatment of PPH; MgSO$_4$ injection for prevention and treatment of severe pre–eclampsia and eclampsia; ampicillin, gentamicin and metronidazole injections for treatment of maternal sepsis; ampicillin, gentamicin, procaine benzylpenicillin, and ceftriaxone for neonatal sepsis; and contraceptives including oral, emergency, injectable, and implant formulations. In this study, we focused on three medicines – oxytocin, ergometrine, and MgSO$_4$ – for which data were available and consistently reported for all seven countries. We also collected information pertaining to the availability of calcium gluconate – the recommended antidote for MgSO$_4$ toxicity – whenever the relevant data were reported.

Data

The data in each country report consisted of observations, interviews and archival analysis. For each country, a collaborative team of researchers from WHO, UNFPA, the Ministry of Health (MoH), and local representatives conducted site visits. Interviews were conducted with local partners and stakeholders such as representatives from the MoH, professional organizations, pharmaceutical administration authorities, reproductive and maternal health non–governmental organizations (NGOs). Documents relevant to the use of medicines were also reviewed. Examples of

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relevant documents included, but were not limited to, national essential medicine lists, standard treatment guidelines and protocols, training manuals, procurement policies and reports, commodity security status assessment reports, and national health strategic plans.

The following data were collected for each medicine: (1) need and demand, (2) availability, (3) presence on essential medicine lists, (4) inclusion in standard treatment guidelines and protocols, (5) rational use, (6) licensing and areas of quality assurance, (7) storage, (8) procurement and supply chain, (9) costs, and (10) coordination and integration between public and private collaboration efforts.

Fishbone (Ishikawa) diagram as the analytic framework and assessment tool

The Ishikawa diagram is also known as the "fishbone" or "cause and effect" diagram. It was developed by Kaoru Ishikawa in 1968 and is well known in the quality management, quality control, and manufacturing industry [15]. The Ishikawa diagram shows a visual representation of potential causes contributing to an overall outcome. Recently, it has been used as an analytic tool in the health sciences field. In 2010, Ridge et al. proposed the development and use of this diagram to rapidly assess the barriers and facilitators to the availability and use of $MgSO_4$ in Zambia [16]. In 2013, Bigdeli et al. used this diagram as the conceptual framework to identify health system barriers to access and use of $MgSO_4$ in Pakistan [17].

In this study, we used the fishbone Ishikawa diagram that Ridge et al. developed to assess the barriers and facilitators to quality use of three essential medicines – oxytocin, ergometrine, and $MgSO_4$. For each medication, Ishikawa diagrams of facilitators and barriers were created and modified using an iterative process based on the data extracted from each country report.

The four health system levels influencing barriers and facilitators to the quality use of essential medications were defined as: (1) government/regulatory, (2) pharmaceutical supply system, (3) health facility, and (4) and health professional [16]. We extracted data from the country reports that were specific to these four levels. At the government/regulatory level, we collected medication–specific information regarding inclusion in essential medicine lists, medicine licensure, and recommendations in national and local standard treatment guidelines. At the pharmaceutical supply system level, we extracted information regarding procurement and supply procedures for each medication. At the health facility level, we collected data regarding access to care and the equipment and supplies necessary for diagnosing procedures and drug storage. Lastly, at the health professional level, we extracted data associated with health providers' knowledge and practice. All extracted textual data relevant to each of the four health–system levels proposed in our analytic framework were recorded in Excel.

We interpreted and fitted the extracted data from the seven reports into the appropriate categories in the Ishikawa diagram. **Table 1** shows the categories that were used to summarize extracted data.

Availability of medicines

Each report recorded the number of health care centers and medicine–supply facilities visited, as well as whether each of the three medicines was available at each facility on the day of visit. We calculated the availability of an individual medicine as the percentage of facilities where each medicine was reported as available on the day of data collection. Because its availability and timely administration is crucial to reverse $MgSO_4$ toxicity, we also calculated the availability of calcium gluconate [18].

Data presentation

We present the availability data and Ishikawa diagrams for each medicine. We provide a qualitative summary of the facilitators and barriers derived from the Ishikawa diagrams.

Ethical approval

Because this study was a secondary analysis of published reports, institutional review board (IRB) approval was not required.

Table 1. Components required for the quality use of an essential medicine by health system level

Government/regulatory level	Pharmaceutical supply system level	Health facility level	Health professional level
• Included in the essential medicine list • Quality–assured medicine licensed for use in country • Recommended treatment in national standard treatment guideline • Standard treatment guideline translated into suitable local protocol	• Suitable procurement procedure in place • Medicine supplied to health care facility	• Woman have access to care (antenatal care or skilled birth attendants) • Equipment and supplies available for diagnosis of complications and drug storage • Correct diagnoses are made	• Health providers aware medicine is first–line treatment • Staff trained to use medicine • Trained staff available to administer medicine • Equipment and supplies are available to administer medicine

RESULTS

Availability

Availability of the three medicines varied by country and medicine (**Table 2**). Oxytocin had high availability in six out of seven countries compared to ergometrine. The two exceptions were the Philippines and the Solomon Islands, where ergometrine was available in a higher percentage of facilities than oxytocin. Four countries had $MgSO_4$ available at less than 60% of their facilities, with only 18% of health facilities carrying $MgSO_4$ in Laos. Calcium gluconate, a required antidote for $MgSO_4$ toxicity, was not consistently available when $MgSO_4$ was present.

Facilitators and barriers to quality use of medicines

Figures 1 and **2** show the fishbone diagrams of the facilitators and barriers for oxytocin as examples. Fishbone diagrams for all medicines are available in the **Online Supplementary Document**. **Table 3** summarizes the analysis from the fishbone diagrams and shows the facilitators and barriers to the availability and use of oxytocin, ergometrine, and $MgSO_4$ across all four health–system levels. The section below describes the barriers and facilitators at each level of analysis: regulatory/government, pharmaceutical supply system, health facility and health professional.

1. Regulatory/Government Level

Oxytocin. Oxytocin is the WHO recommended uterotonic drug for the prevention and treatment of PPH [10,12]. Oxytocin was included in the essential medicine lists (EML) of all seven countries. Indications for use were included in the EMLs of six countries, with the exception of the Philippines. A functional drug registration system in compliance with WHO–Good Manufacturing Practices guideline existed in all countries except the Solomon Islands. Data for oxytocin licensing status was not consistently reported across all seven countries. However, none

of the oxytocin formulations were licensed in Laos. Standard treatment guidelines recommended oxytocin as a first line medicine for prevention of treatment of PPH in Laos, DPRK, and the Philippines. In contrast, Vanuatu and the Solomon Islands recommended ergometrine or syntometrine (combination of oxytocin and ergometrine) as a first–line drug treatment, which was not consistent with WHO evidence–based recommendations. Across all seven countries, standard treatment guidelines were inconsistent, out–of–date, and not widely disseminated.

Ergometrine. Ergometrine is the second–line recommended uterotonic drug for prevention and treatment of PPH when oxytocin is unavailable or when bleeding does not respond to oxytocin [10]. The use of ergometrine is limited by its side effects and contraindication in patients who have high blood pressure. In Mongolia and the Solomon Islands, ergometrine was not listed on the national EMLs. Ergometrine was licensed for use in three countries (Nepal, DPRK, the Philippines). Ergometrine and syntometrine were recommended as first–line drugs for PPH in Vanuatu and on the Solomon Islands, respectively. Standard treatment guidelines for prevention and treatment of PPH and the use of ergometrine were unavailable or not updated according to the most current WHO clinical guidelines.

$MgSO_4$. $MgSO_4$ injection is recommended for the prevention and treatment of eclampsia in women with severe pre–eclampsia [9,12]. $MgSO_4$ was included as an essential medicine in the national EMLs of all seven countries. Indications were clearly provided with the exception of the Philippines. In Laos, the recommended formulation (50% solution) was not found to be licensed or available; 20% and 15% formulations were observed in facilities. DPRK was the only country which reported translating and utilizing treatment guidelines for pre–eclampsia and eclampsia in partnership with WHO, UNFPA, and other national professional associations. Overall, at health facilities, there was a lack of treatment guidelines, treatment protocols, and educational materials for the management of this pregnancy complication.

Table 2. Availability of medicines by country

	AVAILABILITY OF MEDICINE (% OF FACILITIES)†						
	Laos (n = 34)	Mongolia (n = 39)	Nepal (n = 26)	DPRK (n = 11)	Philippines (n = 40)	Vanuatu (n = 6)	Solomon Islands (n = 16)
Medicine							
Oxytocin	50	85	89	73	70	100	69
Ergometrine*	n/r	51	54	n/r	73	83	88
$MgSO_4$	18	95	58	82	55	33	86
Calcium gluconate	n/r	69	39	n/r	35	0	72

DPRK – Democratic People's Republic of Korea, n/r – not reported

*Syntometrine (combination of oxytocin and ergometrine) on Solomon Islands.

†The availability of an individual medicine was calculated as the percentage (%) of facilities where each medicine was reported as available on the day of data collection.
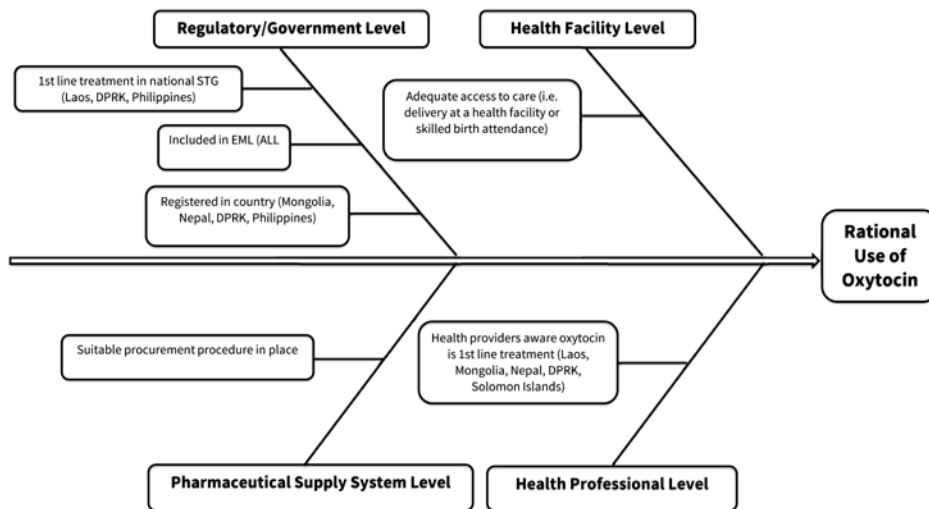
Figure 1. Facilitators to the availability and use of oxytocin.
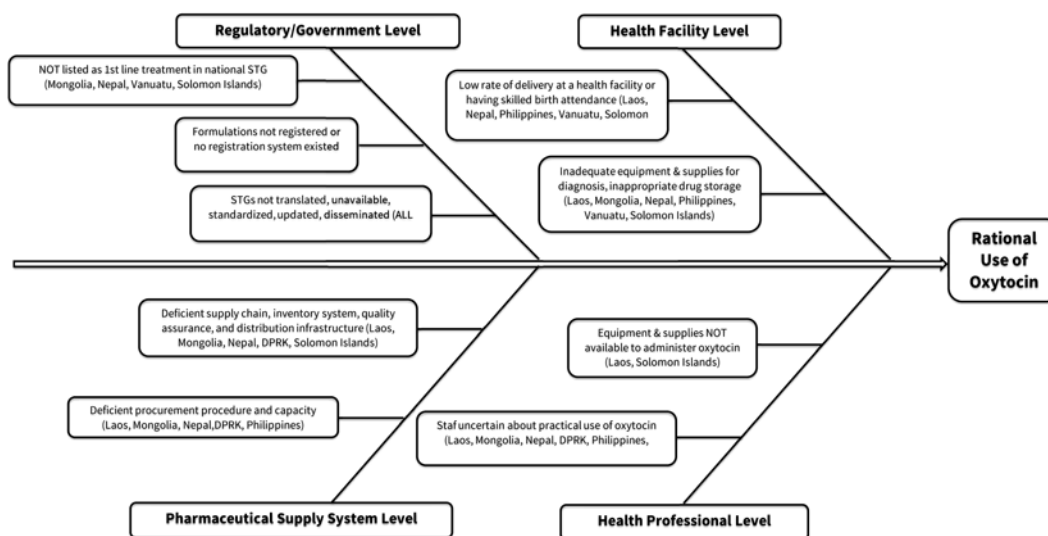
Figure 2. Barriers to the availability and use of oxytocin.

Table 3. Summary of facilitators and barriers to the availability and use of oxytocin, ergometrine, and MgSO$_4$

HEALTH SYSTEM LEVEL	FACILITATORS	BARRIERS
Government/Regulatory	Essential medicine included in the national EML	• STGs for pre–eclampsia/eclampsia and PPH prevention and treatment were not consistent, updated, or disseminated • Ergometrine and syntometrine recommended as first–line for PPH prevention and treatment • Formulations not licensed by national drug authority • No drug registration system
Pharmaceutical supply System	Essential medicine listed on the national EML	• Lack of adequate and suitable procurement and forecasting system in place • No stringent quality assurance process, especially storage conditions to maintain drug efficacy • Inadequate infrastructure led to stock–outs in health facilities
Health facility	Essential medicines found in health facilities	• Wide variation in the level of availability between different countries • Lack of stringent requirements for maintenance of equipment used to store medications • Lack of adequate diagnostic testing equipment to make correct diagnosis
Health professional	Health professionals aware of recommended first–line medicines for PPH and pre–eclampsia/eclampsia prevention and treatment	• Uncertainties in the practical administration of essential medications • Lack of continuous professional education for health providers • Lack of equipment to safely administer medications

2. Pharmaceutical supply system level

The reports identified commonalities across countries regarding the procurement of oxytocin, ergometrine, and $MgSO_4$. First, procurement of drugs was based on each country's EML. Second, there was a lack of accurate, consistent, and scientific methods to estimate and forecast the use of medicines. Last, there was a lack of resources and capacity to optimize the procurement process. Package inserts or drug labels provided inadequate, non–specific information, and were sometimes written in languages not widely understood in the country, such as English, Russian, Thai, or Chinese. Additionally, a majority of countries reported an inadequate supply chain due to inconsistency in inventory (ie, stock card management), delay in supply leading to stock–outs (ie, from agencies that donated essential medicines), or an inadequate infrastructure and lack of transportation to health facilities. Vanuatu was the only country found to have a well–integrated procurement mechanism and supply system for essential medicines. Structured and standardized forms and drug order lists were available for use both in public and NGO facilities.

3. Health Facility Level

Oxytocin. Giving birth in an environment where trained health providers such as doctors, nurses, or midwives are available (skilled birth attendants) can help provide timely medical interventions to prevent complications and death. A majority of the countries reported having 15% to 38% of births delivered without skilled birth attendants. In Laos and Nepal, a high percentage of births took place at home, 85% and 81% respectively. In the Philippines, a higher number of deliveries with skilled birth attendants occurred in urban vs rural areas. On the Solomon Islands, about 15% of births were assisted by nurse aides with the least amount of in–service training.

Additionally, Laos and the Solomon Islands reported a lack of diagnostic equipment for PPH. Expired drugs and stock–outs were observed in health facilities in Vanuatu and the Philippines.

The storage condition of oxytocin was widely reported as inappropriate. Oxytocin is a heat–sensitive medicine and must be kept at 2–8°C. Reproductive health kits, which contained oxytocin, were stored at room temperature. In addition, the cold chain requirements for this medication were at risk due to unstable power supply or inadequate maintenance of refrigerators.

Ergometrine. Results pertaining to skilled birth attendance and availability of diagnostic equipment were similar to findings reported for oxytocin. Ergometrine also has restricted storage conditions. It is a light–sensitive medica-tion, but was stored inside the delivery room, unpacked, and exposed to sunlight.

$MgSO_4$. Receiving antenatal care allows for early detection, management, and prevention of hypertension during and after pregnancy. The percentages of women who did not receive antenatal care ranged from 75% in Laos to 16% in Vanuatu. Antenatal care was provided to 99% of women in DPRK and 95% on the Solomon Islands. In Laos, several health centers lacked adequate equipment to do urine and haemoglobin testing in order to make correct diagnosis for patients with severe pre–eclampsia. The lack of diagnostic equipment as well as equipment to administer $MgSO_4$ safely was also reported in primary health centers on the Solomon Islands, even though a high percentage of health facilities (86%) had the medication in stock. Calcium gluconate, a required antidote for $MgSO_4$ toxicity, was not available in many facilities across all seven countries.

4. Health professional level

Oxytocin. There was a relatively high level of awareness of the need to use oxytocin for every delivery as part of the active management of third stage of labor (AMTSL) in most countries assessed. However, other treatments were sometimes preferred over the use of oxytocin (ie, ergometrine, syntometrinecarbazochrome). There were also uncertainties as to when to administer the drug, what the maximum dose was, and whether it should be administered in combination with ergometrine. Health professionals were unaware of the correct storage conditions for the medication.

Ergometrine. Ergometrine alone or ergometrine/oxytocin combination was recognized as the first–line medication for prevention and treatment of PPH in Vanuatu and the Solomon Islands, even when WHO recommendations for prevention and treatment of PPH stated that oxytocin should be the drug–of–choice uterotonic agent.

$MgSO_4$. Health professional awareness of the use of $MgSO_4$ was adequate in Laos, Mongolia, and Nepal. Nevertheless, in Mongolia, Vanuatu, and the Solomon Islands there was uncertainty about how $MgSO_4$ should be administered. Furthermore, a lack of equipment to safely administer $MgSO_4$ was seen in Laos and the Solomon Islands.

DISCUSSION

The "fishbone" Ishikawa diagram was used as the analytic framework to describe the findings of rapid assessments of essential medicines for maternal health conducted in seven countries. We identified common facilitators and barriers to the availability and use of oxytocin, ergometrine, and $MgSO_4$ across 4 health system levels: (1) government/regulatory, (2) supply system, (3) health facility, and (4) and health professional.

Facilitators

The first common facilitator at the government policy level was that all three essential medicines were consistently listed on national EMLs. This was an encouraging finding as oxytocin, ergometrine, and MgSO$_4$ were listed on the WHO EML [11]. The WHO Model List of Essential Medicines is developed based on the following criteria: prevalence of diseases, efficacy and safety of treatment recommendations, and comparative cost–effectiveness analysis [19]. In the past three decades, it has been increasingly used within national health systems to ensure adequate supply, appropriate dosages, formulations, and indications. Adapting the WHO EML into a national EML is highly encouraged. In fact, it has been argued that having a functional EML is a "strong indicator" of an effective health system since it provides guidance for adequate procurement and supplies of medicines in a particular country [20]. National EMLs should therefore be more integrated into procurement procedures in each country to ensure consistent supply of essential medicines at all time.

Our second common facilitator was identified at the health professional level. We found that there was generally high knowledge, awareness, and acceptance of essential medicines as first–line treatment options for PPH and pre–eclampsia/eclampsia. Knowledge of a medicine is a necessary prerequisite to using it [21]. Additionally, a high awareness and acceptance of the use of essential medicines, especially by local opinion leaders can promote evidence–based practice and facilitate the adoption of clinical practice guidelines [22].

Barriers

We identified major barriers to use of the medicines in each health–system level evaluated, particularly in areas related to standard treatment guidelines, drug procurement, drug supply and storage, and staff training.

First, it was consistently reported that there was a lack of local standard treatment guidelines for the management of pre–eclampsia/eclampsia and active management of the third stage of labor. The lack of guidelines could reasonably be accounted for by the lack of translation of WHO treatment guidelines into suitable local guidelines or by a lack of an adequate dissemination mechanism for guidelines and their derivative products, such as teaching materials, posters, and visible treatment flowcharts. A positive example of the successful translation of guidelines to suitable local protocols was observed in DPRK. In this country, WHO guidelines for maternal and child health were translated and printed. The content of derivative products, such as posters, was consistent with WHO guidelines. This finding shows that collaboration with international organizations such as WHO and UNFPA to promote the use of suitable standardized treatment guidelines should be encouraged in order to assist health care providers in their treatment decision–making process.

Second, a suitable procurement process was generally not in place due to inadequate capacity for forecasting essential medicines or a lack of documentation of procurement procedures. However, there was evidence that a few countries, such as Vanuatu and the Solomon Islands, had better stock maintenance, inventories, and ordering systems in place. Training programs for personnel that focus on drug procurement and supply are crucial in ensuring adequate and consistent access to essential medicines. These training programs can be aimed towards pharmacists who play an important role in the drug supply cycle [23]. The pharmacy workforce, however, is still lacking and underutilized in many low income countries [23,24].

Third, even when the assessed medications were available, issues surrounding the presence of an antidote or the appropriate storage of the medications were a concern. It is unclear why calcium gluconate, an antidote for MgSO$_4$ toxicity, was not stored and whether practitioners were aware of its indication. In addition, oxytocin was not properly stored at a temperature between 2–8°C. This was most likely explained by three factors: (1) lack of refrigerators, (2) pharmacists not aware of the storage condition, and (3) insufficient information printed on package inserts. Provision of the necessary equipment to store medication is extremely important if these medications are to be efficacious when administered to patients. Pharmacists as well as other providers such as physicians, midwives, nurses, and technicians must be aware of the storage conditions for oxytocin. Moreover, drug information labels must be required to provide specific information regarding the storage of medications. In situations where oxytocin is not present or cannot be safely administered by a skilled birth attendant, the WHO EML and WHO guideline for prevention and treatment of PPH recommend the administration of misoprostol, which does not have any storage limitations [10,11]. However, a 2012 survey of 43 countries found that less than one third of the countries had misoprostil available [25].

Last, across all health care professions – physicians, pharmacists, nurses, and midwives – there was a considerable knowledge–practice gap. With oxytocin, even though most health care providers were aware of treatment guidelines, they were not aware of how oxytocin should be used. Continuous education programs and active workshops promoting new standard practice guidelines should be developed and required for all health professionals to enhance hands–on training with these essential medicines.

LIMITATIONS

A few limitations should be noted in our study. During these rapid assessment exercises, country–specific health facilities were purposefully chosen to minimize constraints due to time limitations, transportation, and human capacity from both the investigators and the local authorities. Therefore, the report findings may not be representative of all health facilities in each country or in all low resource countries. Second, data were extracted from secondary sources (ie, reports), instead of the primary data sources (ie, interview transcripts). Access to the primarily data sources could have provided more information for the Ishikawa diagrams. In addition, the findings of our study may not reflect the most up–to–date use of essential medicines for maternal health in the assessed countries. Lastly, the data were collected at a specific point in time and the barriers and facilitators could vary over time in each country.

Despite these limitations, using the fishbone diagrams as an analytic tool allowed us to identify common barriers and facilitators to the quality use of essential medicines at different health–system levels in seven countries. Follow–up studies could develop and evaluate tailored intervention programs that specifically address these barriers to quality use of these life–saving medicines [26].

CONCLUSIONS

The "fishbone" Ishikawa diagram is a useful tool for describing the common facilitators and barriers to the quality use of essential medicines for maternal health across countries. The diagram highlighted the complexity between and within each health–system level that must function to ensure the availability, access, and appropriate use of medicines. The specific facilitators and barriers identified should guide the development of tailored intervention programs to improve and expand the use of these life–saving medicines.

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Impact of global health governance on country health systems: the case of HIV initiatives in Nigeria

Charles Chikodili Chima, Nuria Homedes

The University of Texas Health Science Center at Houston, School of Public Health, Houston, Texas, USA

Background Three global health initiatives (GHIs) – the US President's Emergency Plan for AIDS Relief, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the World Bank Multi–Country HIV/AIDS Program – finance most HIV services in Nigeria. Critics assert that GHIs burden fragile health systems in resource–poor countries and that health system limitations in these countries constrain the achievement of the objectives of GHIs. This study analyzed interactions between HIV GHIs and the Nigerian Health System and explored how the impact of the GHIs could be optimized.

Methods A country case study was conducted using qualitative methods, including: semi–structured interviews, direct observation, and archival review. Semi–structured interviews were held with key informants selected to reach a broad range of stakeholders including policymakers, program managers, service providers, representatives of donor agencies and their implementing partners; the WHO country office in Nigeria; independent consultants; and civil society organizations involved in HIV work. The fieldwork was conducted between June and August 2013.

Findings HIV GHIs have had a mixed impact on the health system. They have enhanced availability of and access to HIV services, improved quality of services, and strengthened health information systems and the role of non–state actors in health care. On the negative end, HIV donor funding has increased dependency on foreign aid, widened disparities in access to HIV services, done little to address the sustainability of the services, crowded out non–HIV health services, and led to the development of a parallel supply management system. They have also not invested significantly in the production of new health workers and have not addressed maldistribution problems, but have rather contributed to internal brain drain by luring health workers from the public sector to non–governmental organizations and have increased workload for existing health workers. There is poor policy direction, strategic planning and coordination, and regulation of externally–financed HIV programs by the government and this poses a great limitation to the optimal use of HIV–specific foreign aid in Nigeria.

Conclusions A few reforms are necessary to improve the strengthening effect of GHIs and to minimize their negative and unintended consequences. This will require stronger leadership from the Nigerian government with regards to better coordination of externally–financed health programs. Also, donors need to play a greater role in addressing the negative consequences of foreign aid. The findings highlight important unintended consequences and system–wide impacts that get little attention in traditional program evaluation

Correspondence to:

Charles Chikodili Chima, MBBS, DrPH, MSc
Healthcare Transformation Initiatives, The
University of Texas Health Science Center at
Houston
1200 Binz Street, Suite 730
Houston, Texas 77004, USA
chimacharles@gmail.com

The immense suffering that has characterized the AIDS pandemic and other disease epidemics in low and middle–income countries led to the emergence of several global health initiatives (GHIs) in response to these deadly diseases. These GHIs have brought significant attention and massive resources to global public health [1]. For example, although donor funding generally constitutes less than 10% of total health care expenditures in Nigeria, the majority of AIDS spending – up to 85% in most years – has been donor funded [2,3]. Three Global Health Initiatives (GHIs) – the US President's Emergency Plan for AIDS Relief (PEPFAR); the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund); and the World Bank Multi–Country HIV/AIDS Program have contributed most of these external funds [2,3]; more than four billion US dollars since 2001 (**Table 1**). In their effort to scale up services for diseases of interest such as HIV/AIDS, GHIs can either support countries to strengthen their weak public health systems in general (horizontal approach) or take a focal approach that prioritizes service delivery for the disease of interest, including the establishment of parallel health systems and processes if necessary (vertical approach). The latter approach dominates the GHI global health funding architecture [4]. Hence, despite their successes in scaling up critical services for targeted diseases, GHIs have been criticized especially for unintended consequences attributable to their vertical orientation and the resource constraints in the recipient countries. They have been noted to burden weak health systems in the recipient countries, by bypassing existing country systems and creating parallel and duplicative processes [1,5,6]. Secondly, the inherent weaknesses in the recipient country health systems, such as inadequate health care infrastructure, health workforce shortages, and poorly developed supply chain management systems, health information systems, and governance architecture limit the ability of GHIs to achieve their objectives [1,5,7–9]. Furthermore, while they might strengthen the capacity of health systems to respond to the HIV/AIDS epidemic, they might weaken their ability to respond to the needs of the entire population by diverting scarce resources to a particular disease area. Rather than fostering the unending age–long debate on horizontal vs vertical approaches to donor funding [4,10,11], empir-

ical assessment of the impact of donor funding initiatives will be more helpful, to both donors and recipient countries, in identifying ways to optimize the impacts of such vital donor funds.

Empirical evidence of the country consequences of GHIs is limited and most of the single country studies on GHI–health system interactions have focused on individual GHIs, especially the Global Fund [12–15]. There has not been an in–depth assessment of the impact of GHIs on the Nigerian health system. Country situations differ widely in the sense that health systems are complex and their organization and performance are highly context–specific [1]; hence findings from other countries may not be entirely applicable to Nigeria. This study assessed the country–specific interactions and system–wide impact of the three aforementioned GHIs on the Nigerian health system, so as to provide information to policy makers and development partners on how to maximize the synergies between the GHIs and the country's health system.

METHODS

A country case study was conducted using qualitative methods, including: semi–structured interviews, direct observation, and archival review. Semi–structured interviews, lasting 45 to 90 minutes, were held with 36 key informants selected through purposive sampling, as well as by snowballing, to reach a broad range of stakeholders including policymakers, program managers, and service providers at different levels of the health system (federal, State, and local); representatives of donor agencies and their implementing partners (IPs); the WHO country office in Nigeria; independent consultants; and representatives of civil society organizations involved in HIV work (**Table 2**). Respondents provided written consent and all procedures were reviewed and approved by the research ethics committee of the authors' institution and a locally relevant ethical board at the country of study. The respondents were assured confidentiality and anonymity; hence they were assigned a secret code that we used to identify the information and statements they provided. Several open–ended questions were asked of each respondent; however the in-

Table 1. HIV donor disbursements to Nigeria

GHI	Year of first grant to Nigeria	Disbursements (as at 31 March 2014)
World Bank MAP*	2001	US$ 221.48 million
Global Fund†	2003	US$ 433.91 million
PEPFAR‡	2004	>US$ 3.4 billion

*Source: World Bank Project and Operations – Nigeria, http://www.worldbank.org/projects/search?lang=en&searchTerm=&themecode_exact=88.
†Source: Global Fund Data Site, http://web–api.theglobalfund.org/DataAnalysts/Index.
‡Source: PEPFAR disbursement data are not publicly available. Figure is based on information from US Embassy Nigeria, http://nigeria.usembassy.gov/pepfar.html.

Table 2. Mapping of key informants

Stakeholder group	Number of interviewees
Government Representatives – Ministries and Agencies at the federal, state and local government levels:	
– Directors, policy makers, and other higher level managerial staff	4
– Project managers, program officers and other mid–level positions	8
Development partners: HIV/AIDS Global Health Initiatives and WHO Country Office	5
International NGOs/contractors	6
Local NGOs and contractors, and independent consultants	8
Advocacy groups	1
Public facility providers	3
Faith–based health care providers	1
Total	36

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terview guide was flexible to capture the unique knowledge of each interviewee. The interviews were conducted between June and August 2013, when permitted they were recorded, and otherwise handwritten notes were taken. The interviews were transcribed, coded using ATLAS.ti (v 7.1.7), and analyzed using a thematic analysis approach.

The findings from the interviews were checked against field notes from direct observation and extensive archival review. This triangulation minimized the potential for biases arising from recall failure or individual idiosyncrasy. The review included documents obtained through individual contacts and web–based searches. Included among these were strategic and operational plans, grant applications and project completion reports, and other relevant documents from organizations involved in HIV program funding and implementation in Nigeria; including the National Agency for the Control of AIDS (NACA), the Federal Ministry of Health (FMOH), National Primary health Care Development Agency (NPHCDA), the Global Fund, World Bank, PEPFAR, USAID, and The US Centers for Disease Control and Prevention (CDC). The approach also involved direct observation of meetings between implementing partners and government bodies, policy and planning meetings of government agencies, and visits to a couple of donor–supported Antiretroviral Therapy Clinics.

The case study approach is the best method for in–depth social science research [16] and was considered the most appropriate to extensively explore contextual influences on the interactions and impact of HIV GHIs on the Nigerian health system.

RESULTS

Findings on the impact of donor–funded HIV programs on health system building blocks, as defined by the WHO, are presented below and summarized in **Table 3**.

Leadership and governance

Also known as stewardship, the leadership and governance function manages the other building blocks to achieve the objectives of the system. Key leadership and governance functions include policy guidance, regulation, system design, and accountability [17]; the impact of HIV donor funding is discussed along these lines.

System design. A crucial leadership function is to design the governance architecture in a way that ensures fit between strategy and structure and minimizes duplication and fragmentation [17]. As we will see, the stewardship of the Nigerian health system has failed to come up with an organizational design that achieves this purpose.

At the national level, there are several agencies responsible for coordinating development assistance and providing leadership for HIV programs. These are the National Planning Commission (NPC), National Agency for the Control of AIDS (NACA), the HIV/AIDS Division of the Ministry of Health (formerly the National AIDS/STI Control Program – NACSP), and the Global Fund Country Coordinating Mechanism (CCM) which oversees all Global Fund grants. To worsen the situation, these agencies and organizational units communicate poorly and their responsibilities overlap.

The NPC's mandate is to manage and coordinate development aid and technical assistance from international development partners (Respondent 29 [R–29]). It approves initiatives that foreign entities want to conduct in Nigeria, including HIV programs. Unfortunately there is poor communication and coordination between the NPC and the line ministries; hence the interactions between donors working in the health sector and the NPC do not necessarily get communicated to the Ministry of Health and vice versa (R–10; R–29) (see Quote 1, **Online Supplementary Document**).

Two major entities share the leadership of HIV programs: NACA and NASCP. NACA is tasked with coordinating the multi–sectoral response to HIV in Nigeria, which means bringing together the activities of the Ministry of Health, other ministries and government agencies, as well and the work of donor agencies and non–state actors to form one single 'national response' to HIV. NASCP on the other hand is tasked with overseeing the response of the health sector to the HIV epidemic in Nigeria, including granting approv-

Table 3. Analysis framework and summary of key findings

Health system building block	Themes	Major findings
Leadership and governance	System design, policy guidance and regulation, health sector accountability, civil society participation, dependency	• The country has not done a good job at coordinating donor funded programs for HIV • The coordinating infrastructure for HIV foreign aid is chaotic and not integrated with the health system • Because of the absence of strong policy direction, strategic planning, and regulation by the government, GHIs take a self–directed approach and do things as they deem fit • HIV GHIs have strengthened the role of non–state actors in health care • Donor funding has deepened a culture of dependency on foreign aid
Health information systems	Data availability, data demand and use	• HIV donor funding has strengthened information systems in the health sector • The culture of proper records keeping and data gathering has rubbed off positively on the system • HIV donor funding has improved the availability of good quality health information through population health surveys • Because of political constraints, improvements in availability of health data have not necessarily translated to increased utilization of data in program planning and implementation in the public sector
Human Resources for Health	Training; retention, distribution, and brain drain; workload, motivation and incentives	• GHIs have generally not invested significantly in the production of new health workers • PEPFAR is increasingly investing in pre–service training to improve the quality of health workers • The system is experiencing a training overload • The trainings are rarely evaluated for impact • Per diems have created disincentives for learning in the system: people go to trainings with the hope of 'getting paid' rather than to build their capacity • Activities of HIV GHIs have not positively affected the shortage of human resources for health in rural areas in tangible ways • A new trend in medical brain drain is emerging whereby health workers are lured away from the public sector to non–governmental or private sector organizations or projects funded by GHIs • HIV donor funded programs have increased workload for existing health workers by failing to invest in manpower recruitment • Though there are no salary differentials between health workers of the same cadre working on HIV programs and those working elsewhere, however those working on HIV programs typically have more opportunities for professional development and other benefits
Financing	Domestic allocations and sustainable financing	• Domestic allocations for HIV program delivery have generally been abysmal, as the government has practically handed over financing of HIV services to donors • Recently though, the President committed in July 2013 to scale up government's financial commitment by launching the president's comprehensive response plan (PCRP) for HIV/AIDS in Nigeria • The achievements made in HIV service delivery over the past decade is not sustainable as the current system cannot afford to continue deliver the services free of charge when donor funding ceases
Service delivery	Physical infrastructure, quality, equity and coverage, access and uptake, spillover effect	• HIV programs generally deliver services of higher quality than the rest of the system • An HIV donor funded initiative – The National Alliance for Health Systems Strengthening (NAHSS) – is working with the Federal Ministry of Health to develop a National Quality Improvement program (NigeriaQual) • Aid implementing agencies trade equity for efficiency when making service delivery decisions • Access to HIV services has increased but uptake has not been optimal • Best practices in patient care and follow–up in HIV program settings have impacted on other health services positively • HIV program scale–up crowded out delivery of non–HIV health service in the emergency phase of the AIDS response, however by strengthening health infrastructure HIV donor funds have also positively affected the delivery of other health services
Supply management systems	Procurement and distribution	• HIV GHIs have led to the development of a parallel procurement and supply management system • The elimination of fragmentation in the supply management system for HIV has reduced stock outs • The supply management system is not sustainable as it is run by a consortium of foreign technical organizations supported by donor grants

GHI – Global Health Initiative, PEPFAR – US President's Emergency Plan for AIDS Relief

al to donor implementing partners (IPs) to carry out HIV programs in health facilities. Thus, there is overlap between the duties of NASCP and the NPC, and because of NACA's overreaching nature (R–9; R–10; R–12) the roles of NASCP vs NACA are also unclear (R–12) (see Quote 2, **Online Supplementary Document**).

The Global Fund requires recipient countries to establish CCMs to oversee Global Fund grants in their respective countries. However, the Principal Recipient (PR) of a Global Fund grant is the institution with whom the grant agreement is signed and remains the entity legally responsible for the execution of the contract [18]. The PR is responsible

for grant implementation, monitoring and reporting and it is accountable to the CCM. By becoming a Global Fund grant recipient, thus making it accountable to the CCM, NACA is derailing from its coordination mandate and becoming more of an implementing agency.

NACA and its equivalents at the State level – State Agencies for the Control of AIDS (SACAs) – have been greatly strengthened by donor funds, and they are now the most visible government players in HIV program delivery, while the Ministries of Health at the Federal and State levels increasingly lag behind (R–19; R–35). The idea of creating a body (NACA) independent of the ministry of health to oversee the national response to HIV was to overcome the bureaucracies in the ministry that militate against timely program implementation (R–2, R–19). However the creation of this parallel coordinating structure negatively impacts the sustainability of the programs (R–1) (see Quote 3, **Online Supplementary Document**). In summary, the governance of HIV programs in Nigeria is chaotic (**Figure 1**).

For PEPFAR funds, PEPFAR agencies in Nigeria, namely the CDC country office, the USAID, and the US Department for Defense, are under the control of the country PEPFAR coordinator domiciled at the US Embassy in Nigeria. These institutions manage their own funds, activities, and processes (R–12; R–13; R–30).

Policy guidance and regulation. Collectively, the responsible government units have done a poor job at developing clear policies; formulating sector strategies; defining goals and directions; and identifying and managing the roles of donor agencies and their IPs, and other actors in the Nigerian health sector (R–9; R–12) (see Quotes 4 and 5, **Online Supplementary Document**). The result of this government failure is that donors do things as they deem fit. For instance, the selection of facilities that will be equipped to deliver HIV

services has mostly been based on where the donor agencies identify the right infrastructure for them to meet their project metrics in a timely manner (R–8; R–19; R–35).

The problem of poor donor coordination is even worse at the State level, as State governments have limited capacity for strategic planning (R–25) (see Quote 6, **Online Supplementary Document**).

Health sector accountability. Generally speaking, donor funding for HIV programs has not had much impact on strengthening accountability in the public sector (R–5) (see Quote 7, **Online Supplementary Document**). Though, by strengthening civil society, donor funding is contributing to building of mechanisms for checks and balances in the health system (R–25).

Strengthening of civil society. In general, HIV GHIs have strengthened the role of non–state actors in health care in Nigeria. Most of PEPFAR funding is channeled through non–state actors, although many of them are international non–governmental organizations (NGOs). The first round of HIV grant from the Global Fund was specifically designed to promote the effective participation of civil society organizations (CSOs) in the national response to HIV/AIDS. The World Bank has also promoted the participation of CSOs in the implementation of HIV programs [19]. CSOs help build accountability and keep the system honest through interventions in quality assurance and by independent confirmation of the data reported by HIV program implementing partners. For example, one of the CSOs – the Network of People Living with HIV/AIDS in Nigeria, NEPWHAN – uncovered gaps in access to HIV services at public facilities; including human resource issues like health worker absenteeism and impolite behavior (R–25).

Notwithstanding the positive contribution of CSOs, there have been legitimate concerns about insufficient account-
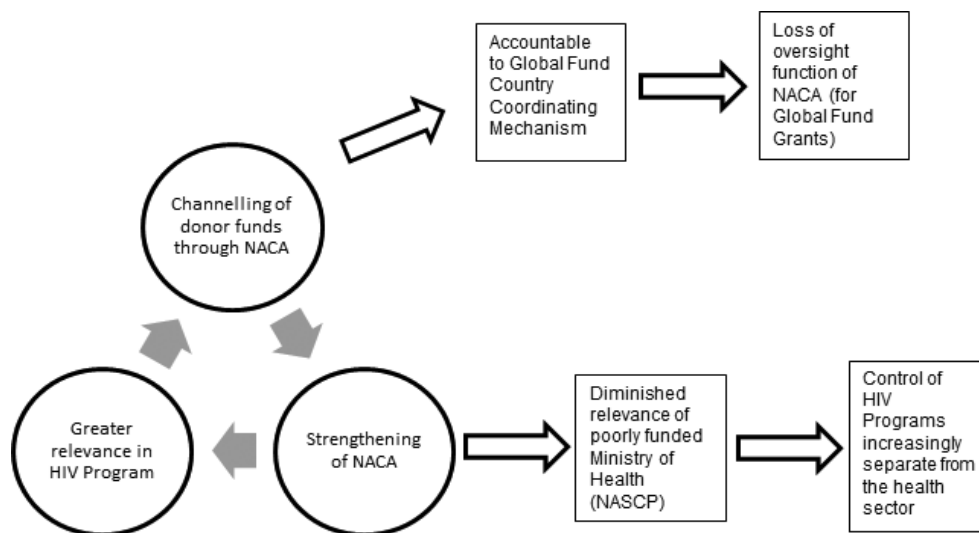
Figure 1. Impact of Channeling of Donor Funds through NACA on Governance of HIV Programs in Nigeria.

ability, legitimacy, and transparency within such organizations [20], and similar concerns exist in Nigeria (R–25) (see Quote 8, **Online Supplementary Document**). The industry is poorly regulated.

Dependency. There is no doubt that donor funding for HIV has saved many lives in Nigeria but respondents believe that it has harmed the system by preventing the government from developing capacity and home–grown solutions to the HIV/AIDS epidemic (R–1; R–19; R–35). The role of GHIs is supposed to be to help fill funding gaps and provide limited technical assistance but some government units at different levels happily relinquish responsibility for the HIV epidemic to USAID and CDC (R1; R–12; R–19).

Health information systems

A robust health information system (HIS) is one that ensures the production, analysis, dissemination and use of reliable and timely health information by decision–makers [17]. Here we document the impact of GHIs on data availability and data demand and usage by decision makers.

Data availability. Due to the absence of necessary data management systems, the electronic Nigerian National Response Information Management System (eNNRIMS) was created to pool and track data from health facilities to be able to monitor and evaluate HIV/AIDS services. There are ongoing efforts to integrate this system with the other data systems in the health sector to form a single national routine HIS that will become a go-to source of health data, under the leadership of the government [21] (R–14). Hence, HIV funding could potentially strengthen the country's HIS. At the moment however, integration has only being achieved within the HIV program; other programs – malaria, tuberculosis, etc. – have their own independent health information systems [21].

Besides the eNNRIMS District HIS, the culture of data gathering in compliance with monitoring and evaluation requirements for donor funded programs has rubbed off positively on the system. Most respondents attested to this fact (see Quote 9, **Online Supplementary Document**). Non–routine health data sources, such as population health surveys, have also strengthened data collection efforts in Nigeria (R–14).

Data demand and use. Despite the increase in capacity to collect and interpret health metrics, improvements in availability of health data have not necessarily translated into increased utilization of data for policy formulation or health program planning in the public sector (R–19) (see Quote 10, **Online Supplementary Document**).

Human Resources for Health

Nigeria has several human resources for health (HRH) challenges including severe shortages and maldistribution.

Shortage of qualified health workers in rural areas is particularly a problem [22, 23]. The critical shortage of health workers in Nigeria is worsened by a serious medical brain drain problem [22–25]. Low quality and quantity of human resources are known to militate against achievement of the objectives of GHIs [26], and there is concern that GHIs place significant burden on health care workforce [1,5]. We assessed the impact of donor–funded HIV programs on the availability and performance of health workers in Nigeria.

Training of health workers. Due to growing concerns that human resource shortages were limiting the impact of GHIs in developing countries, PEPFAR decided to finance the Medical Education Partnership Initiative (MEPI) – a five year health workforce development grant to 13 Medical Schools across Africa [26]. MEPI has a total worth, across all the recipient schools and countries, of US$ 130 million and is funded through the Office of the US Global AIDS Coordinator and the National Institutes of Health (NIH). The aim of the grant is to increase retention of doctors in the regions where they train and to address the persisting problem of maldistribution of health workers [26,R–5] by increasing the quality and quantity of medical graduates in the recipient schools and strengthening the research capacity of faculty by developing their ability to write and manage research grants. A consortium of six Nigerian medical schools applied for and is implementing MEPI. So far, MEPI has not increased the capacity for production of new health workers in Nigeria but it has impacted positively on the system in other ways, especially by strengthening research capacity [26,R–5] (see Quote 11, **Online Supplementary Document**).

Another major way that HIV donor funding has impacted positively on the Nigerian health workforce has been through in–service training. Most of the trainings are focused on issues related to HIV treatment, although some deal with other issues such as financial management, supply chain management, and integrated service provision for primary health workers. Nearly all respondents pointed out this fact as a positive impact of HIV donor funding; however several concerns were also raised. Many of the respondents were of the opinion that the system is experiencing a training overload (see Quote 12, **Online Supplementary Document**). A second issue is that the trainings are rarely evaluated for impact (R–12; R–28) (see Quote 13, **Online Supplementary Document**). The finding of lack of evaluation of training programs was corroborated by a recently concluded assessment of in–service training of PEPFAR programs in Nigeria [27]. Third, the hotel–based nature of the trainings with their associated per diems has created disincentives for learning in the system. For many health workers, the trainings have become a way to top up their salary rather than avenues to improve their knowledge and skills.

Thus people have developed ways to defraud the system (R–7) (see Quote 14, **Online Supplementary Document**).

Retention, distribution, and brain drain of human resources. Maldistribution is one for the major challenges with health worker availability in Nigeria. A clinical program director noted that "Our problem is … retention and maldistribution. Many of the medical graduates leave and the ones that stay back reside in the urban areas, leaving rural people uncared for"(R–5). Activities of HIV GHIs have not positively affected the shortage of health workers in rural areas in tangible ways. This is unlike the situation in some other countries, like Zambia for example, where PEPFAR has funded a rural retention scheme that provides incentives to attract health workers to rural areas [28]. On the contrary, donor funded HIV programs in Nigeria have negatively impacted the maldistribution problem; in some instances State governments have redistributed health workers from facilities without donor-funded projects to ones where projects are to be sited in order to meet the minimum requirement of the development partner (R–8) (see Quote 15, **Online Supplementary Document**).

Also, the majority of HIV donor programs are situated in secondary and tertiary health care facilities, and these happen to be mostly in urban areas. Hence the programs might be further widening the divide between health care for urban and rural people.

Besides MEPI, there has not been much direct action by HIV GHIs to address the problem of poor health worker retention in Nigeria. On the contrary, most respondents agreed that with the advent of GHIs, a new trend in medical brain drain is emerging whereby health workers are lured away from the public sector to non–governmental or private sector organizations or projects funded by GHIs (see Quote 16, **Online Supplementary Document**).

Workload, motivation and incentives. Generally, donor funded HIV programs do not cover the salaries of health workers. This is particularly the case for public sector facilities, where most of the respondents working for donor agencies or their IPs see it as the responsibility of governments to hire and pay health workers. In a few occasions however, IPs showed willingness to provide funding to private–for–profit and faith–based health facilities to augment their staff strength (R–16; R–27).

The few health workers in public facilities that receive donor support for HIV programs are left to bear the consequences of the increased workload consequent upon HIV treatment expansion without a corresponding increase in the number of human resources (R–5) (see Quote 17, **Online Supplementary Document**).

There are no salary differentials between health workers of the same cadre working on HIV programs and those working elsewhere. However, those working on donor funded HIV programs typically have more opportunities for professional development through participation in capacity building workshops and, as mentioned earlier, monetary incentives are often given for such trainings in the form of per diems (R–9; R–13). The unequal incentive system has negatively impacted on collegiality and motivation in some instances, as people working on less funded programs felt less appreciated (R–9).

Financing

Domestic allocations. The federal government piloted a national HIV treatment program in 2002 but never scaled it up, possibly due to the advent of PEPFAR and Global Fund shortly afterwards. As these GHIs became increasingly active in the country, the government handed over, almost totally, the financing of HIV services to these initiatives (R–1; R–5; R–17; R–19), with augmentation from two rounds of loans from the World Bank.

As a result since the year 2000, more than 85% of HIV expenditures have been donor funded. However it appears that the situation has begun to change, at least on paper. In August 2010, the Government of the United States (USG) signed a Partnership Framework on HIV/AIDS with the Government of Nigeria (GON) [29]. One of GON's stipulated responsibilities in this agreement is to increase the proportion of GON financing for HIV/AIDS from 7% in 2008 to 50% by 2015. In line with this agreement, the President of Nigeria committed in July 2013 to scale up government's financial commitment by launching the President's Comprehensive Response Plan (PCRP) for HIV/AIDS. The PCRP has been praised as Nigeria's own counterpart to PEPFAR (R–2, R–12, R–30). It aims to bridge gaps and establish a framework for achieving targets for HIV control by 2015 [30]. If fully implemented, it is projected that the PCRP will push domestic expenditure for HIV to 60% of total funding by 2015, but there is no evidence yet that the government is living up to this huge commitment.

Sustainable financing. The HIV delivery system has been described by many as a "*Cadillac System*" in the sense that donor funding has enabled the scale up of high quality services at minimal cost to the system and at almost zero cost to the end users in an environment where access to basic health services remains a big challenge. These short–term gains risk not be sustained if donor funding winds down. This is worrisome considering that globally, the growth rate of donor funding for health slowed dramatically in the recent past [31] (R–14). The sustainability issue was the elephant in the room throughout most interviews. Across the board, there was a consensus that the current aid–dependent model was not sustainable (R–1; R–19; R–24; R–25; R–28; R–30; R–35; R–36).

Service Delivery

The impact of HIV donor funding on service delivery is presented under five important themes: physical infrastructure; quality; equity and coverage; access and uptake; and spillover effect on non–HIV health services.

Physical infrastructure. A significant portion of HIV funding has been invested in infrastructural support to health facilities, ministries of health, and other government agencies. These funds have been used to rehabilitate dilapidated buildings and build new ones, purchase vehicles, and develop Information and Communication Technology systems. Laboratories in donor supported sites have particularly benefited from HIV funding (R–5; R–7; R–11) (see Quote 18, **Online Supplementary Document**).

Quality. Quality of health care is notably poor in Nigeria. The system is still dealing with fundamental issues of access to basic lifesaving interventions, and monitoring and enhancing service quality is not yet on the policy table. Nonetheless, HIV care and treatment stands out from the rest of the health sector due to the influence of the resources and monitoring systems made available through donor funding.

The facilities receiving support for HIV services from donor IPs are accountable to these organizations and receive supervisory visits from them (R–4; R–11); hence even in situations where things might not be working well in other sections of a hospital or clinic, providers have to maintain certain standards when they provide HIV services. This has resulted in better quality of HIV services and may have had a positive spillover effect on the system (see Quote 19, **Online Supplementary Document**].

The Nigerian Alliance for Health Systems Strengthening (NAHSS), a PEPFAR–funded project that is being implemented through the CDC with the University of Maryland as a partner, is supporting the Federal Ministry of Health to develop a National Quality Improvement program (NigeriaQual). NAHSS aims to strengthen the capacity of local indigenous health organizations, States and health facilities to integrate quality improvement activities into organizational, financial and program planning activities, as well as into HIV care and treatment services at facilities [32] (R–20).

Spillover effect on mon–HIV health services. HIV programs have promoted the upholding of international best practices in HIV care and some of these have had system–wide impacts beyond the care of HIV patients. A good example is patient care coordination and follow up to improve adherence to treatment (see Quote 20, **Online Supplementary Document**).

There is concern that the spillover effect of HIV could be weakening health systems in developing countries by diverting attention and scarce resources in the health sector, especially human resources for health, towards HIV pro-grams [33]. In the case of Nigeria, some respondents felt that the HIV program was not big enough to lead to such effect (R–12; R–35) but a couple of them disagreed (see Quote 21, **Online Supplementary Document**).

Equity and coverage. Aid implementing agencies were accused of caring less about ensuring equitable distribution of health services than about ensuring that they get good project numbers quickly, even at the expense of equity (R–8; R–19, R–35). This view was corroborated by the director of an international NGO (R–17) (see Quote 22, **Online Supplementary Document**). It is ironical that the facilities that are doing better tend to be selected for more support, because such 'viable facilities' are more likely to quickly scale up services with minimal support (R–35) (see Quote 23, **Online Supplementary Document**). This approach has resulted in gross inequities in the distribution of HIV services in Nigeria.

Another aspect of equity involves taking cognizance of and addressing socioeconomic barriers to accessing HIV services. Courtesy of donor funding, HIV treatment is provided mostly free at the point of service in most centers in Nigeria. Hence, affordability at point of service is not a major barrier to equitable access to HIV services.

Access and uptake. Although HIV/AIDS prevention, care and treatment services have dramatically increased, a persisting challenge is to attract the people who need these services to the facilities. As at December 2012, only 30% of the estimated 1.6 million Nigerians in need of antiretroviral therapy (ART) were receiving it [30]. In addition, a recently published UNAIDS report indicated that Nigeria has the largest number of children acquiring HIV infection from their mothers – nearly 60 000 cases in 2012 – and suggested that the country was not on track to meeting global targets by 2015 [34].

Respondents had different perspectives on the major reasons for poor uptake of the 'free' HIV services, including poor engagement of the private sector (R–28), poor awareness and insufficient demand–side interventions (R–21), and persisting stigma against people living with HIV (R–30).

Supply management systems

The majority of HIV commodities, especially test kits and antiretroviral drugs, are purchased through PEPFAR or Global Fund support. The quantification of needs is done in unison for the entire country by all relevant stakeholders, including government agencies and development partners. After the quantification is done, PEPFAR and Global Fund then procure their share of supplies to fulfill the needs of all HIV programs in the country.

In Nigeria, PEPFAR procures HIV commodities through a project known as the supply chain management system,

SCMS, whereas the Global Fund uses the Voluntary Pooled Procurement (VPP) system [35] (R–36). The procurement systems for HIV commodities are parallel to the procurement schemes for the rest of the health sector. The system for distributing HIV commodities is also dedicated to the HIV program and independent of the rest. Whereas most other commodities are moved from the federal level to regional/state level stores from where they are distributed to the facilities, the HIV program eliminates intermediary steps (R–31) (see Quote 24, **Online Supplementary Document**). This challenge poses a limitation for integration with the supply chain system for other health commodities.

The Supply Chain Management System (SCMS) Project. The Partnership for Supply Chain Management, PF-SCM, a consortium established by JSI Research & Training Institute, Inc. (JSI), and Management Sciences for Health (MSH) runs a PEPFAR–funded supply chain project for HIV commodities known as the supply chain management system (SCMS). Prior to 2012, various PEPFAR IPs were not only managing the implementation of HIV treatment services in facilities but also handling the distribution of HIV commodities. For better coordination and efficiency USAID/USG decided to unify supply chain management across its various partners. So SCMS now pools procurement for the various IPs and ensures distribution from manufacturer to the service delivery points (R–24; R–31).

After receiving approval from PEPFAR agencies, SCMS embarked on an exercise to bring the entire supply chain system for HIV commodities under its control, using a handful of strategically located regional hubs. Very importantly, the unification exercise was eventually transformed to become a national project, involving not only USG–affiliated organizations but also the Global Fund and the Government of Nigeria. So as it stands now, the distribution of HIV commodities for the entire country is handled entirely by SCMS. It also handles procurement for USG partners (PEPFAR financed) but the Global Fund still does its own procurement (R–31).

SCMS has significantly improved the availability of HIV commodities in Nigeria. Stock outs have been reduced appreciably (R–13, R–24), and it is likely that they have also harnessed economies of scale and improved on cost-effectiveness. However, SCMS has derailed from its original mission in Nigeria, which consisted of strengthening supply chain systems and building local capacity for logistics management through technical assistance (R–12; R–31). Instead the supply management system has become outsourced; rather than teaching locals how to do the job, SCMS has taken over the job (R–12; R–36). Most respondents familiar with the supply management system lambasted the current arrangement and stressed the need for a transition plan by which SCMS returns back to its tech-

nical assistance mission and transfers responsibility for operations to the public sector through the Federal Medical Store and the Federal Ministry of Health.

Despite its successes, the current procurement and supply chain management system is not sustainable (R–24; R–30; R–36) (see Quote 25, **Supplementary Online Document**).

DISCUSSION

HIV/AIDS GHIs have had mixed effects on the Nigerian health system

HIV GHIs have had a mixed impact on the health system. They have enhanced availability of and access to HIV services, improved quality of services, and strengthened health information systems and the role of non–state actors in health care. On the negative end however, they have increased dependency on foreign aid; widened disparities in access to HIV services; done little to address the sustainability of the services; and led to the development of a parallel supply management system. They have also not invested significantly in the production of new health workers and have not addressed maldistribution problems, but have rather contributed to internal brain drain by luring health workers from the public sector to non–governmental organizations and have increased workload for existing health workers. There is poor policy direction, strategic planning and coordination, and regulation of externally–financed HIV programs by the government and this poses a great limitation to the optimal use of HIV–specific foreign aid in Nigeria. A couple of reforms are needed to improve the ability of HIV–specific foreign aid to strengthen the Nigerian health system. We look at these from the perspective of reforms needed on the part of the Nigerian government and the issues that donors need to address to improve the effectiveness of their investments.

The Nigerian government should start leading

A major limitation to the optimal use of HIV donor funding in Nigeria is the fact that 'the government is not leading'. Nigeria is an example of how poor coordination at the national level limits the ability of GHIs to strengthen health systems. As Vayrynen [36] once wrote, "…global governance cannot replace the need for good governance in national societies; in fact, in the absence of quality local governance, global and regional arrangements are bound to fail or will have only limited effectiveness". The Nigerian government needs to do a better job at developing clear sector strategies and policies, identifying and managing the role of donor agencies and their IPs, and seeking avenues to increase domestic allocations for health. This is unlike the situation in some other African countries like Ghana, where

the government sets clear policies with regards to development assistance for health, provides policy guidance, and regulates the activity of donors through a sector–wide approach that prevents parallel financing and delivery structures [12].

The first challenge is that control of the national HIV program resides outside of the health sector, causing duplication and wastage. NACA was established as a separate institution by the Presidency in a bid to achieve quick–wins in its response to the AIDS epidemic. Now that the emergency phase of the AIDS response is over, its future role should be addressed in the context of a general reform of the Federal Government that has a lot of parallel agencies and commissions that duplicate duties of ministries. The HIV/AIDS division of the Ministry of Health (NASCP) needs to be strengthened to play a central role in HIV program delivery in Nigeria; especially since most activities of the HIV program are based in the health sector.

Secondly, with regards to managing official development assistance (ODA), there is a need for better delineation of duties between the National Planning Commission (NPC), and line ministries and government agencies. The Ministry of Health should be given the responsibility for managing and coordinating ODA specifically intended for health programs. On the other hand, in conjunction with the Ministry of Finance, the NPC should be responsible for collating information on ODA across all government sectors and helping the executive arm of government to strategically incorporate ODA into national planning and budgeting. Clear communication processes and expectations should be set between NPC and ministries; one solution could be for each ministry to have liaisons at the NPC and vice versa, such that there is a constant channel for exchange of information regarding all ODA inflows and their utilization.

Thirdly, there is a dire need for strengthening health systems at local and regional levels. The country has a three–tiered system of government, namely Federal (National), State, and Local governments. For a country as big as Nigeria with 36 States, some with populations greater than many other African Countries, the importance of regional and local leadership cannot be overemphasized. Although HIV services have been significantly scaled up in the last decade as a result of which more than 500 000 Nigerians are now on antiretroviral therapy (ART) [30], the scale–up has not been done in an equitable manner and uptake has not been optimal. There are still 60 000 vertical transmissions of HIV in the country every year [34], and more than one million people living with HIV/AIDS eligible for ART are not yet on treatment [30]. There is need for a system–wide gap analysis at the state and local government levels to accurately map out areas and/or populations not being reached by services and devise strategies to address the gaps. Government leadership will be crucial in this regard

and this will help donors to play a better role of filling the gaps in the system. State governments also need to do a better job of coordinating donor activities in their respective States for optimal outcomes.

The fourth needed reform is in the area of health information systems. HIV donor funding has improved the availability of good quality health data, however the reporting systems in the health sector are fragmented and would immensely benefit from integrating the various disease–specific platforms. Hopefully, ongoing initiatives in this direction will be sustained to ensure the establishment of a single robust health information system run by the Ministry of Health.

Finally, a plan for sustainability of HIV services in Nigeria needs to be articulated by the government, with donor support where possible. This will entail action in three major areas among others: increasing budgetary allocations, development of risk–pooling mechanisms for financial protection, and seeking market interventions to bring down the cost of HIV commodities to affordable levels. In April 2001, Nigeria and other countries in the African Union made a commitment to allocate at least 15% of their annual budgets to the health sector [37], however in the ten years following this pledge, Nigeria's average government expenditure on health as a percentage of total government expenditure remained poor at 6.7% [38]. The recent launch of the Nigerian President's Comprehensive Response Plan for HIV/AIDS, scheduled to run from 2013 to 2015, promises to increase the government's contribution to HIV financing. The impact of this initiative on country ownership of the HIV program should be assessed in follow–up studies. An equally important sustainability issue is the need to address Nigeria's lack of effective risk pooling mechanisms for health care financing. Donor agencies can provide financial and technical support to the government to strengthen and scale up the National Health Insurance Scheme as this will be crucial to the sustenance of the access to good quality services that have been promoted by GHIs. Finally, market–shaping interventions to increase access to essential health commodities, such as those championed by the Clinton Health Access Initiative and UNITAID, would go a long way in ensuring the ability of host governments to sustain HIV services in the event of decreased donor funding.

Donors should invest more in systems strengthening and encourage country ownership

Donors have been criticized, and often rightly so, for caring more about achieving specific project–related metrics and less about the system–wide and long–term impacts of expenditures for health in recipient countries. Yet, it will take robust health systems to sustain the gains of billions

of dollars of global health finances into the future. For example, the MEPI program which aims to strengthen health workforce in select countries in Africa only received 130 million dollars from PEPFAR contrasted to the billions it has spent on direct service delivery across the continent. As the prevailing dominant model of global health financing, GHIs can lead by example by prioritizing and emphasizing the strengthening of health systems in countries where they operate. In Nigeria in particular, the issues of access to health workers in rural areas remains a huge problem. GHIs should sponsor a rural retention scheme that provides tangible incentives to attract health workers to rural areas. There is also over–concentration of donor programs in secondary and tertiary facilities than primary health care facilities. The bias of secondary and tertiary health care towards urban areas mean that the rural–urban divide in access to good quality health services is further widened by donor intervention. Hence GHIs will do greater good by channelling increased resources to the strengthening of primary health care systems

Development jobs opened up by HIV donor agencies and their implementing partners may be helping to retain physicians and other health workers in the country, through the private sector. However, a good number of such jobs are non–clinical public health positions, so the impact on access to clinicians may be the same as if the providers had left the country. A more detailed study of this phenomenon would be necessary to characterize the magnitude and nature of the internal brain drain in other to proffer solutions. One approach could be by compensating the public sector for the internal brain drain by funding health worker recruitment and retention.

There is a need to conduct an impact evaluation of the health workforce in–service training programs. The few systems strengthening efforts of GHIs have focused heavily on such capacity building programs, yet there is a glaring absence of efforts to ascertain if and how these activities have improved the quality of health workers in Nigeria. Implementing partners should also transit from the current hotel–based in–service training approach to an institution based one whereby they collaborate with tertiary institutions and teaching hospitals to conduct on–the–job trainings without pulling the health workers away from their place of work. This will eliminate disincentives and resource wastages and refocus attention to a sustainable culture of continuing medical and nursing education.

GHIs should show more interest in the sustainability of the programs they finance by promoting country ownership. In Nigeria for example, PEPFAR should promote country ownership of the supply chain management system for the procurement and distribution of HIV commodities. The national unification project for HIV supply chain championed by SCMS has reduced fragmentation, increased efficiency, and decreased wastage. For these achievements to have lasting impacts beyond the duration of the contract for the SCMS project, JSI and its partners need to begin to lay greater emphasis on technical assistance to build the capacity of government staff at the Federal Medical Store in Lagos, and the various regional hubs and zonal stores. In 2012, a National Product Supply Chain Management Program was established under the department of food and drug services in the Federal Ministry of Health with the mandate to coordinate the logistics of various disease–specific programs in the health sector to ensure the minimization of stock outs and wastage of health commodities. This government unit, which is still in an infant stage, needs all the support possible from both the government and development partners so that it can grow and positively impact the system by building synergies across the various parallel supply chain systems for health commodities.

In conclusion, the impact of HIV GHIs on Nigeria's health system has been mixed. This case study highlighted the importance of context in the debate about the system–wide effects of GHIs on country health systems, and offered practical solutions to some of the observed challenges.

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Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta–analysis

Ting Shi[1*], Kenneth McLean[1*],
Harry Campbell[1,2†], Harish Nair[1,3,4†]

[1] Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK

[2] Centre for Population Health Sciences, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK

[3] Centre for Medical Informatics, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK

[4] Public Health Foundation of India, New Delhi, India

[*] Joint authors in this position.

[†] Joint authors in this position

Background Acute lower respiratory infection (ALRI) remains a major cause of childhood hospitalization and mortality in young children and the causal attribution of respiratory viruses in the aetiology of ALRI is unclear. We aimed to quantify the absolute effects of these viral exposures.

Methods We conducted a systematic literature review (across 7 databases) of case–control studies published from 1990 to 2014 which investigated the viral profile of 18592 children under 5 years with and without ALRI. We then computed a pooled odds ratio and virus–specific attributable fraction among the exposed of 8 common viruses – respiratory syncytial virus (RSV), influenza (IFV), parainfluenza (PIV), human metapneumovirus (MPV), adenovirus (AdV), rhinovirus (RV), bocavirus (BoV), and coronavirus (CoV).

Findings From the 23 studies included, there was strong evidence for causal attribution of RSV (OR 9.79; AFE 90%), IFV (OR 5.10; AFE 80%), PIV (OR 3.37; AFE 70%) and MPV (OR 3.76; AFE 73%), and less strong evidence for RV (OR 1.43; AFE 30%) in young children presenting with ALRI compared to those without respiratory symptoms (asymptomatic) or healthy children. However, there was no significant difference in the detection of AdV, BoV, or CoV in cases and controls.

Conclusions This review supports RSV, IFV, PIV, MPV and RV as important causes of ALRI in young children, and provides quantitative estimates of the absolute proportion of virus–associated ALRI cases to which a viral cause can be attributed

Correspondence to:

Dr. Harish Nair
Centre for Global Health Research
Usher Institute of Population Health Sciences and Informatics
University of Edinburgh
Medical School, Teviot Place, Edinburgh EH8 9AG, UK
Harish.Nair@ed.ac.uk

Acute lower respiratory infection (ALRI), including pneumonia, remains the leading cause of childhood hospitalization and mortality in young children (under 5 years old) [1], primarily within developing countries [2]. It has been previously estimated that there were 11.9 million and 3.0 million respective episodes of severe and very severe ALRI that contributed to childhood hospitalization globally in 2010 [3]. Furthermore, there were 0.935 million attributable deaths in 2013 [4].

Streptococcus pneumoniae and *Haemophilus influenza type b* (Hib) have been established as the principal aetiological agents of pneumonia – together thought to cause over 50% of all severe ALRI cases in developing countries [5]. The childhood vaccination programme against these bacteria [6] is associated with a substantial reduction in morbidity and mortality from ALRI [7]. Continued research is required to further understand the role of other ALRI pathogens, such as viruses.

Respiratory viruses are implicated, either directly, or as synergistic pathogens or co–factors in bacterial superinfections, in up to two thirds of all cases of pneumonia (equating to 80 million cases in young children in 2010) [2,8]. Respiratory syncytial virus (RSV) is the most commonly identified virus in young children with ALRI, contributing to an estimated 33.8 million new cases globally in 2005 [9]. Also, at least 25 other viruses have been associated with ALRI in children, most notably – rhinovirus, influenza, human metapneumovirus (MPV) and parainfluenza viruses (PIV) [8]. However, their aetiological role in ALRI in young children remains uncertain and we are not aware of any systematic reviews currently published that investigate this.

Therefore, it is important to understand these viruses' contribution to ALRI. We aimed to conduct a systematic review to identify all case–control studies investigating the potential role of respiratory viruses in the aetiology of acute lower respiratory infections in children younger than five years of age.

METHODS

Search strategy and selection criteria

We conducted and reported a systematic review according to the PRISMA guidelines. We used tailored strategies to search Medline, Embase, Global Health, LILACS, China National Knowledge Infrastructure (CNKI), Wanfang Data and Chongqing VIP databases (**Online Supplementary Document**). We further hand–searched the table of contents of specialist journals – the *Influenza and Other Respiratory Viruses* and *Pediatric Infectious Diseases Journal* – and the reference lists of relevant papers for eligible articles. All searches were limited to between 1 January 1990 and 4 April 2014, and there were no publication status or language restrictions applied.

We included studies that fulfilled our strict eligibility criteria: studies in children younger than five years; studies investigating clinical pneumonia (or lower respiratory infection) as the primary outcome; studies where respiratory specimens were collected and diagnostic test conducted using valid laboratory tests; case–control studies / prospective cohort studies that reported data in both case and control groups; reporting virus–specific proportions separate-

ly in both groups; studies published between 1 January 1990 and 4 April 2014 (19 March for Chinese databases). We only included studies where the case definition for ALRI (or clinical pneumonia) was clearly defined and consistently applied.

Two investigators (TS and KM) conducted independent English language literature searches and extracted data using standardised data extraction templates. One investigator (TS) whose first language is Chinese performed the search and data extraction from Chinese language databases (CNKI, Wanfang and CQVIP). Any discordance and/or uncertainties regarding relevance or inclusion were arbitrated by HN or HC.

Definitions

We used "ALRI" as an equivalent to clinical pneumonia as our case definition, which also included bronchiolitis. This was to recognise this common manifestation in young children with viral ALRI [10], and the limits of the WHO case definition to reliably differentiate these [1]. ALRI was characterized as cough or dyspnoea with age–related tachypnoea, while severe ALRI was defined as those with cough or dyspnoea with indrawing of the lower chest wall [11], or an acute respiratory infection severe enough to necessitate hospitalisation. The control groups were defined as asymptomatic (with no respiratory symptoms), healthy (asymptomatic with no other symptoms) or upper respiratory tract infection (URTI) (with respiratory symptoms).

Statistical analysis

We standardised the results of all the included studies as odds ratios (ORs) with accompanying 95% confidence intervals (95% CIs), to facilitate interpretation and comparison. We applied a continuity correction of 0.0005 if a virus was detected in one group, but not the other [12]. This allowed calculation of an OR for these instances, and enabled inclusion within subsequent meta–analyses. Furthermore, matched (mOR) and adjusted (aOR) odds ratios were also extracted, where possible. These were used preferentially in subsequent calculations and analyses.

Using STATA (version 11.2), we performed a meta–analysis of virus–specific ORs and reported pooled estimates with corresponding 95% CIs using the random effects model (DerSimonian–Laird method) because these studies do not share common effect size due to methodological heterogeneity [13]. The virus–specific attributable fraction among the exposed (AFE) was used to explore the etiological role of each virus in ALRI patients. This estimates the percentage of (severe) ALRI which can be attributed to each virus, in absolute terms [14], and was calculated as $AFE = 100 \times (OR-1)/OR$ with 95% CIs (from the corresponding OR 95% CIs).

Thus, the percentage of all ALRI cases caused by a given virus can be calculated as overall percentage of ALRI cases positive for that virus multiplied by AFE (adjusted percentage (%a) = crude percentage (%c) × AFE), as used in previous work [15].

RESULTS

We identified 3619 records through literature search of which only 23 studies fulfilled our strict eligibility criteria (**Figure 1**) [15–37]. Fifty–six studies were excluded for a variety of reasons including: no data specific to children under 5 years old (n=10), not fulfilling the case or control definitions (n=5), no applicable data reported for cases and controls (n=32) and other reasons (n=9). The 23 included studies were primarily conducted within developing countries (n=19) (**Table 1**). Among them, 4 unduplicated papers were from one research group in Thailand [20,22,24,37]. And most of the studies have been conducted since 2003 (n=20).

All included studies were case–control studies with an ALRI and asymptomatic/URTI groups; however some variations were still present. Of the case definitions employed, most used ALRI/ARI (n=13), while others used (severe) pneumonia (n=8), SARI (n=1) or bronchiolitis (n=1). All

studies used control group which had no respiratory symptoms, of which 10 were considered otherwise "healthy", and 2 studies [23,25] also reported URTI as control group. Of the case ascertainment used, all articles contained inpatient data. Among them, 3 studies also provided outpatient data [19,21,25]. Twenty controls were ascertained in hospital–based outpatient/clinic sites while 3 were identified in community [15,17,25].

Regarding to sampling methodology, most studies used nasopharyngeal swab (NPS) (n=10), nasopharyngeal aspirate (NPA) (n=6) and nasopharyngeal wash (NPW) (n=1) as specimen. Five studies used mixed specimens including NPA, NPS, lung aspirate and oropharyngeal swab (OPS). All studies used PCR as diagnostic testing except one study from Gambia [16], in which case indirect immunofluorescence (IIF) was applied.

Meta–analyses of virus–specific ORs were reported as well as the corresponding attributable fractions among the exposed (**Table 2**). RSV, IFV (including IFV A), PIV, MPV and RV were significantly more common in children hospitalized with ALRI than asymptomatic controls (OR (95% CI): 9.79 (4.98–19.27), 5.10 (3.19–8.14), 3.37 (1.59–7.15), 3.76 (2.45–5.78) and 1.43 (1.03–1.97), respectively). Thus, these viruses had statistically significant positive AFEs, which show clear associations between these viruses
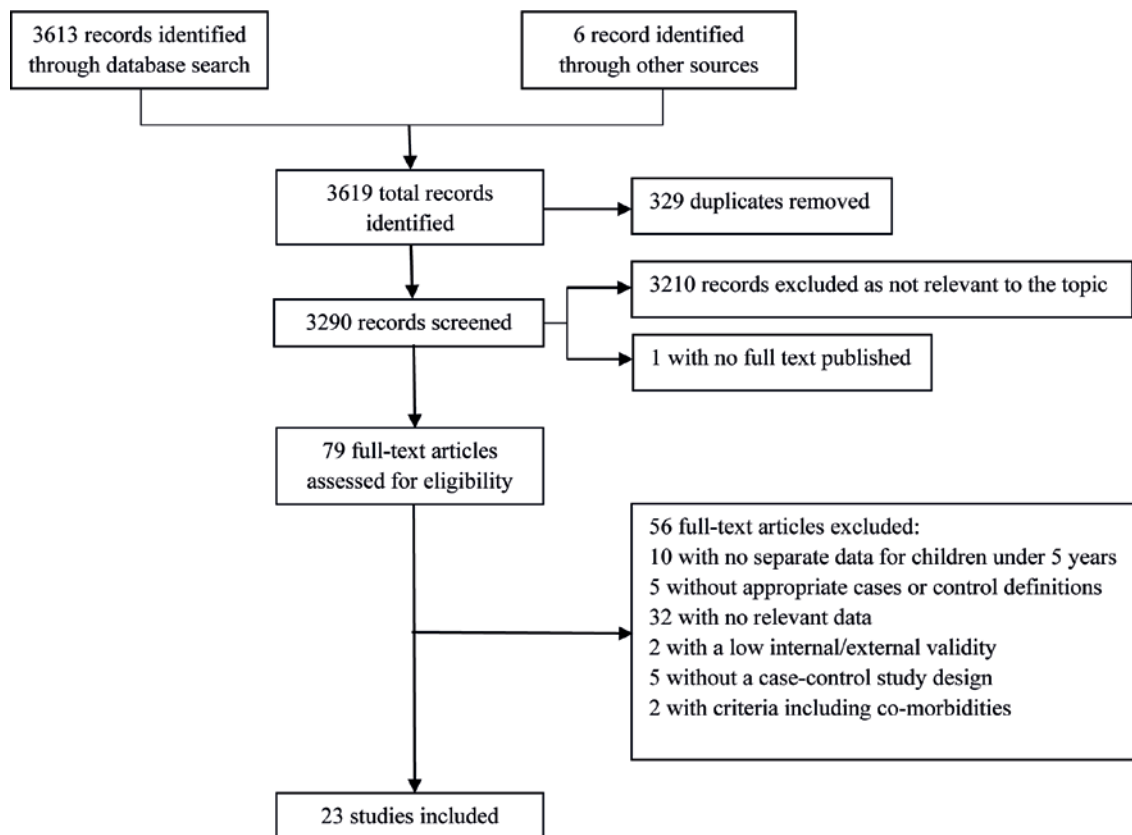
Figure 1. PRISMA flow diagram of the literature search.

Table 1. Characteristics of 23 included studies

Study	Age range	Specimen(s); Diagnostic test(s)	Bacteria tested	Case group n; Ascertainment; Pro (%)	Case group Definition (criteria)	Control Group n; Ascertainment; Sampling method	Control Group Definition (criteria)
Banjul, The Gambia; Periurban; Nov 90 – Oct 92 [16]	3–59 M	NPA, LA; IIF, cell culture	Yes	119; Passive (IP); NS	P (NS)	52; Passive (H) Matched (age, area)	Healthy (No RS or malnutrition)
Baffin Island, Canada; R; Jan 02 – Mar 03 [17]	0–23 M	NPA; ELISA, DFA, m–PCR	No	121; Passive (IP); 91%	ALRI (NS)	119; Active (C); Matched (age)	Healthy (>2W no RS)
Kenya; R; Jan 07 – Dec 07 [18]	0–59 M	NPS; RT–PCR	No	726; Passive (IP); 82%	SP (WHO)	56; Passive (H); Same age group	Healthy (no RS)
Lwak and Kibera, Kenya; R; Mar 07 – Feb 11 [19]	0–59 M	NPS, OPS; qRT–PCR	Yes	538/899#; Passive (IP, OP); 36.9%	SARI (WHO)	193/109; Passive (H); Matched (age)	AS (>2W no RS)
Sa Kaeo, Thailand; R; Sep 04 – Aug 05 [20]	0–59 M	NPS; RT–PCR	No	365; Passive (IP); 50.5%*	P (CXR)	85; Passive (H); Same number in age/month	AS (>3D no RS)
Multicentre, USA; U; Nov (03 – 09) – May (03 – 09) [29]**	0–59 M	NPS; RT–PCR	No	3490; Passive (IP); NS	ARI (NS)	770; Passive (H); Same age, area, study period	Healthy (>2W no RS)
Asembo, Kenya; R; Jan 09 – Feb 10 [21]	0–59 M	NPS, OPS; sq–PCR	Yes	166/33†; Active (C), Passive (IP, OP); NS	SP (WHO)	93; Passive (H); Same age group	AS (>2W no RS)
Sa Kaeo, Thailand; R; Sep 04 – Aug 05 [22]	0–59 M	NPS; RT–PCR	No	369; Passive (IP); 51%*	P (CXR)	85; Passive (H); Same number in age/month	AS (>3D no RS)
Sa Kaeo, Thailand; R; Sep 04 – Aug 05 [37]	0–59 M	NPS; RT–PCR	No	379; Passive (IP); 45%*	ALRI (CXR)	85; Passive (H); Same number in age/month	AS (>3D no RS)
Kilifi District, Kenya; R; Jan 10 – Dec 10 [23]	1–59 M	NPS, OPS‡, IS‡; mRT–PCR	Yes	805; Passive (IP); 84%	SP (WHO)	142/227; Passive (H); Matched (age, month)	AS /URTI (No RS)
Sa Kaeo and Nakhon Phanom, Thailand; R; Jan 05 – Dec 07 [24]	0–59 M	NPS; RT–PCR	No	3809; Passive (IP); NS	ALRI (CXR)	589; Passive (H); Same age group	AS (>3D no RS)
Multicentre, USA; U; Dec 03/Oct 04 – Apr 04/Apr 05 [30]**	0–59 M	NPS; RT–PCR	No	1515; Passive (IP); 83%	ARI (NS)	790; Passive (H); Same age, area, study period	AS (>2W no RS)
Amsterdam, The Netherlands; U; Nov (07–09) – Apr (07–09) [31]**	0–23 M	NPW; mPCR	No	100; Passive (IP); NS	ARI (NS)	59; Passive (H); Same age group	AS (>1W no RS)
Quebec, Canada; U; Dec 02 – Apr 03 [32]**	0–35 M	NPA; qPCR	No	225; Passive (IP); NS	ARI (NS)	100; Passive (H); Same study period	AS (no RS)
Bhaktapur, Nepal; U; Mar 06 – Jul 07 [25]	2–35 M	NPA; mRT–PCR	No	29/671†; Passive (IP, OP); NS	P (WHO)	29/665; Active (C); Matched (age)	AS/URTI (No ab >2D)
Yuedong, China; U; Jan 07 – Dec 07 [28]	0–59 M	NPA; mRT–PCR	No	345; Passive (IP); NS	ALRI (NS)	83; Passive (H); Same age group	Healthy (>2W no RS)
Multicentre, USA; U; Dec 03/Oct 04 – Apr 04/Apr 05 [33]**	0–59 M	NPS; RT–qPCR	No	1481; Passive (IP); 82%	ARI (NS)	742; Passive (H); Same area, study period	AS (>2W no RS)
Stockholm, Sweden; U; Sep 11 – Jan 12 [34]**	0–59 M	NPA; qPCR	No	209; Passive (IP); NS	ARI (NS)	209; Passive (H); Matched (age, time)	AS (>1W no RS)
YK Delta, Alaska, USA; R; Oct 06 – Sep 07 [15]	0–35 M	NPS; sRT–PCR	No	208; Passive (IP); 60%	ALRI (NS)	381; Active (C); Same age group, unmatched	Healthy (>2W no RS)
Beersheba, Israel; U; Nov (01–05) – May (01–05) [36]**	0–59 M	NPW; RT–PCR, DIF, cell culture	No	1017; Passive (IP); 37%	P (WHO)	136; Passive (H); Same study period	Healthy (no RS)
Shantou, China; U; Jun 07 – May 08 [26]	0–24 M	NPA; mRT–PCR	No	271; Passive (IP); NS	B (NS)	82; Passive (H); NS	Healthy (no RS)
Nha Trang, Vietnam; U; Jun 08 – Aug 08 [35]**	0–59 M	NPS; mPCR	No	148; Passive (IP); 97.9%	ARI (WHO)	350; Passive (H); Same age group	Healthy (No RS, No ab >1M)
Shanghai, China; U; Oct 09 – Aug 12 [27]	0–59 M	NPA‡, NPS§; qRT–PCR	No	554; Passive (IP); NS	ALRI (CXR)	195; Passive (H); Random	Healthy (SCDC Sample Bank)

U – Urban; R – Rural, NPA – Nasopharyngeal Aspirate; NPS – Nasopharyngeal Swab; NPW – Nasopharyngeal Wash; OPS – Oropharyngeal Swab; IS – Induced Sputum; LA – Lung aspirate; IF – Immunofluorescence (IIF – Indirect; DIF – Direct); ELISA – Enzyme–linked immunosorbent assay; PCR – Polymerase chain reaction (m – multiplex; RT – reverse transcription; s – singleplex; q – quantitative/real time; (S) P – (Severe) Pneumonia; ALRI – Acute Lower Respiratory Infection; B – Bronchiolitis; NS – Not Stated; RS – Respiratory Symptoms; ab – Antibiotics; Pro – Proportion of eligible cases tested; CXR – Chest Radiography; SCDC – Shanghai Centre for Disease Control; IP – Inpatient; OP– Outpatient; H – Hospital; C – Community; D – Days; W – Weeks; M – Months; AS – Asymptomatic.

*For whole study (all ages).

†Recruitment of IP/OP.

‡Cases only.

§Controls only.

#Recruitment in the respective Lwak / Kibera site.

There were 8 studies which were conducted for less than 12 consecutive months, and a sensitivity analysis was performed excluding these studies which found no significant differences (table in **Online Supplementary Document).

Table 2. The meta analyses of the odds ratios (OR) and attributable fraction in the exposed (AFE) of each virus and its subtype within included studies of inpatient (IP) ALRI cases relative to asymptomatic controls

| Virus | Meta analyses* | | | Sensitivity analyses* | | | | | |
| | | | | Inclusion of symptomatic (URTI) controls | | | Inclusion of outpatient (OP) cases | | |
	n_s	OR (95% CI)	AFE (95% CI)	n_s	OR (95% CI)	AFE (95% CI)	n_s	OR (95% CI)	AFE (95% CI)
RSV:	13	**9.79** (4.98 to 19.27)	**90%** (80 to 95)	13	**8.60** (4.83 to 15.33)	**88%** (79 to 93)	14	**9.59** (5.26 to 17.49)	**90%** (81 to 94)
A	1	–	–	1	–	–	1	–	–
B	1	–	–	1	–	–	1	–	–
IFV:	10	**5.10** (3.19 to 8.14)	**80%** (69 to 88)	10	**3.39** (1.64 to 7.02)	**71%** (39 to 86)	10	**5.54** (3.56 to 8.62)	**82%** (72 to 88)
A	8	**5.97** (3.29 to 10.81)	**83%** (70 to 91)	8	**3.99** (1.68 to 9.49)	**75%** (40 to 89)	9	**6.07** (3.35 to 10.98)	**84%** (70 to 91)
B	9	**2.70** (0.97 to 7.53)	**63%** (–3 to 87)	9	**2.70** (0.97 to 7.54)	**63%** (–3 to 87)	9	**3.36** (1.48 to 7.65)	**70%** (32 to 87)
C	1	–	–	1	–	–	1	–	–
PIV:	11	**3.37** (1.59 to 7.15)	**70%** (37 to 86)	11	**3.14** (1.25 to 7.85)	**68%** (20 to 87)	11	**4.07** (1.91 to 8.67)	**75%** (48 to 88)
1	6	**2.52** (0.79 to 8.07)	**60%** (–27 to 88)	6	**2.10** (0.64 to 6.88)	**52%** (–56 to 85)	6	**3.10** (1.21 to 7.94)	**68%** (17 to 87)
2	7	**2.22** (0.80 to 6.16)	**55%** (–25 to 84)	7	**1.18** (0.33 to 4.27)	**15%** (–203 to 77)	7	**2.34** (0.94 to 5.83)	**57%** (–6 to 83)
3	8	**2.19** (0.97 to 4.97)	**54%** (–3 to 80)	8	**2.05** (0.77 to 5.43)	**51%** (–30 to 82)	8	**4.14** (1.24 to 13.82)	**76%** (19 to 93)
4	1	–	–	1	–	–	1	–	–
MPV	10	**3.76** (2.45 to 5.78)	**73%** (59 to 83)	10	**3.61** (2.38 to 5.46)	**72%** (58 to 82)	11	**3.84** (2.51 to 5.88)	**74%** (60 to 83)
AdV	10	**1.13** (0.71 to 1.80)	**12%** (–41 to 44)	10	**1.16** (0.76 to 1.77)	**14%** (–32 to 44)	10	**1.13** (0.71 to 1.80)	**12%** (–41 to 44)
RV	11	**1.43** (1.03 to 1.97)†	**30%** (3 to 49)	11	**1.41** (1.03 to 1.93)	**29%** (3 to 48)	11	**1.43** (1.03 to 1.97)	**30%** (3 to 49)
BoV	8	**1.20** (0.36 to 3.98)	**17%** (–178 to 75)	8	**1.20** (0.36 to 3.98)	**17%** (–178 to 75)	8	**1.20** (0.36 to 3.98)	**17%** (–178 to 75)
CoV	8	**1.03** (0.80 to 1.33)	**3%** (–25 to 25)	8	**0.94** (0.74 to 1.19)	**–6%** (–35 to 16)	8	**1.03** (0.80 to 1.33)	**3%** (–25 to 25)
HKU1	4	**0.61** (0.34 to 1.09)	**–64%** (–194 to 8)	4	**0.61** (0.34 to 1.09)	**–64%** (–194 to 8)	4	**0.61** (0.34 to 1.09)	**–64%** (–194 to 8)
NL63	5	**0.68** (0.38 to 1.24)	**–47%** (–163 to 19)	5	**0.71** (0.41 to 1.25)	**–41%** (–144 to 20)	5	**0.68** (0.38 to 1.24)	**–47%** (–163 to 19)
229E	4	**1.47** (0.58 to 3.72)	**32%** (–72 to 73)	4	**1.42** (0.46 to 4.43)	**30%** (–117 to 77)	4	**1.47** (0.58 to 3.72)	**32%** (–72 to 73)
OC43	5	**0.91** (0.32 to 2.64)	**–10%** (–213 to 62)	5	**0.84** (0.39 to 1.80)	**–19%** (–156 to 44)	5	**0.91** (0.32 to 2.64)	**–10%** (–218 to 62)

ns – Number of studies; N/A – Not applicable; 95% CI – 95% confidence interval; RSV – Respiratory syncytial virus; IFV – Influenza; PIV – Parainfluenza; MPV – Human metapneumovirus; AdV – Adenovirus; RV – Rhinovirus; BoV – Bocavirus; CoV – Coronavirus; OR – Odds ratio; AFE – Attributable fraction among the exposed.
*From the random–effects model.
†OR=1.40 (1.02 to 1.92) and AFE=28% (2 to 48) when studies testing all other enterovirus are excluded.

and ALRI hospitalization in young children. Therefore, this indicates the potential for substantive reductions in the number of ALRI cases were young children to be vaccinated against these viruses. In comparison, AdV, BoV and CoV were frequently detected in control children, and so did not have significantly positive AFEs. Therefore, their roles in ALRI hospitalisation were uncertain.

Sensitivity analyses were also performed to investigate the effect of inclusion of symptomatic (URTI) controls, and of outpatient ALRI cases (**Table 2**). Data on inclusion of outpatient cases had little impact on the associations observed. However, this does not necessarily indicate similarity between the association of inpatient and outpatient ALRI patients. In comparison, the inclusion of symptomatic controls had a more substantial influence, which reduced the strength of association with every virus, except AdV and CoV–NL63.

DISCUSSION

This is the first systematic review to evaluate and summarise the literature surrounding the viral aetiology of ALRI in young children. Our aim was to summarise good qual-

ity data on the absolute effects of the viral exposure and hence to inform causal inference in ALRI aetiological studies which report respiratory viral data. Our review summarises data from 18 592 cases of ALRI in young children reported across 23 studies. We demonstrated stronger evidence (defined here as a statistically significant OR >3) in support of a causal attribution when a virus is identified in young children presenting with ALRI for RSV (OR 9.59–9.79; AFE 90%), IFV (OR 5.10–5.54; AFE 80%), PIV (OR 3.37–4.07; AFE 70%) and MPV (OR 3.76–3.84; AFE 73%). There was less strong evidence (defined here as a statistically significant OR 1–3) for RV (OR 1.43; AFE 30%). There was no statistically significant difference between viral identification in ALRI cases and controls for the other respiratory viruses studied: AdV, BoV, CoV.

These findings should inform the results of studies which seek to estimate the global / regional / national burden of disease due to these viruses. They support the role of RSV, IFV, PIV and MPV as important causes of ALRI in young children (although disease burden estimates should take into account the AFE estimates that we report – thus the true global burden of RSV/IFV/PIV/MPV pneumonia may be 90%/80%/70%/73% of the values reported in recent

publications). Applying these estimates to the burden of severe (hospitalised) pneumonia in 2010 [38], we estimate that the likely true burden of RSV and influenza associated ALRI for that year would be about 2.9 (95% CI 1.5–5.5) million and 0.8 (0.3–2.2) million respectively. There is considerable international attention on RSV and IFV pneumonia in young children at this time when novel vaccine strategies are being evaluated and prioritised and more accurate disease burden estimates (using these results) would help inform future policies and interventions.

Several methodological issues could affect our results: case ascertainment, case definition, clinical specimen and confounding. Twenty–two of the 23 studies used passive hospital–based case ascertainment. Several previous studies have shown that children in developing countries, particularly those residing in rural areas, have in general, limited access to healthcare [39], and health care seeking behaviour is often delayed or absent [40–42]. This potentially introduced a selection bias. Similarly, only three studies used community based controls [15,19,25]. Hospital ascertained controls may not reflect the general population, and may have other health conditions potentially affecting their viral carriage, especially those with URTI. The ideal control group for these studies would be a random sample of an age and sex matched child population from the same area of residence studied at the same time. Studies, however, recruited controls who were either selected as healthy (asymptomatic) and so biased in favour of those not exposed to the respiratory virus (yielding a falsely high OR) or those who were selected to have respiratory symptoms and so biased in favour of those who had been exposed to the respiratory virus (yielding a falsely low OR). Consistent with this interpretation, we found (**Table 2**) odds ratios (of ALRI given viral identification) to be consistently greater where the control group were "healthy" and asymptomatic rather than symptomatic (URTI). We consider that the value of the OR based on a population–based control group as described above would lie between these two values.

Seven of the included studies [17,20–23,25,36] employed the WHO case definition for pneumonia [43] and this standardised approach enhanced the comparability of results between these studies. These criteria have high sensitivity for pneumonia [44], but lower specificity with overlap with other conditions [45], particularly malaria [46] and wheezing disorders. This tends to inflate the number of "cases" and may contribute to an apparent low level of detection of pathogenic viruses.

All included studies obtained upper respiratory tract specimens (i.e. described as nasopharyngeal secretions, nasopharyngeal wash samples, nasopharyngeal aspirate samples, oropharyngeal samples). Although their differing sensitivities could result in some heterogeneity [47,48],

they are broadly comparable and have common flaws. As viruses identified could be from a coincidental URTI in ALRI cases, the sole use of these specimens can only provide supportive evidence for causality. Lung aspiration is considered the gold–standard sampling technique given it is directly obtained from the infection site [49], which would indicate aetiological significance in ALRI. However, its invasive nature and rate of complications limit its use.

Several potential confounding factors could have distorted the observed associations. Only three studies calculated appropriately adjusted ORs to account for confounding effects from age [24], or age and season [21,23]. Instead, matching of cases and controls was more commonly used – performed by age [16,18,19,25], or age and month [23,34]. Nevertheless, despite the use of matching, no studies maintained this pairing to allow OR meta–estimate calculation. While all studies were conducted on young children (under 5 years), six [15,17,25,26,31,32] were further restricted. As age is an ALRI risk factor [50], this could potentially affect the viral profile detected, introducing further heterogeneity. However, no enough data were provided to estimate the strength of association in narrower age bands.

In addition, multiple aetiological agents may often be identified in young children with ALRI, making the individual contribution of each agent difficult to define. Many of the included studies did not provide virological data that excludes coinfections, so viruses detected in these cases could conceivably fulfil any etiological role. The high sensitivity of polymerase chain reaction (PCR) is important for accurate assessment of aetiological contribution. However, the high rates of viral co–infection detection may overstate the individual contribution [8].

Furthermore, any viruses detected could be from a nascent infection or persistent from a previous infection [51]. These could explain more 'pathogenic' viruses (such as RSV) being identified in asymptomatic children. Some viruses are detectable for weeks before and after ALRI, [52–54] and so the studies only assessing asymptomatic status without considering past or future history may yield false positive findings [16,17,23,32,36].

Moreover, the small sample size [16,25,31], undoubtedly contributed to the imprecise 95% CIs in **Table 2**. This may have also led to the non–detection of statistically significant ALRI–virus associations as in some case and/or control groups. Two studies [15,17] included children of Inuit ancestry from USA or Canada and were found to have high ALRI incidence. The viral associations observed in these two studies may not be generalizable to other populations.

The use of the AFE allows quantification of the excess percentage of ALRI cases due to exposure in absolute terms [55]. However, it assumes the observed association be-

tween the virus (and/or related factors) and ALRI is causal [14], and, in practice, this will undoubtedly have led to extreme estimations. Furthermore, strict interpretation would entail construal of negative values as indicative of the percentage of ALRI prevented by viral exposure [56], which is biologically implausible.

A virus (or any pathogen) can be considered to be associated with ALRI when detected with a significantly higher frequency in cases than controls without respiratory symptom (asymptomatic). However, coincidence, while necessary, is insufficient for proof of a causal role between a virus and ALRI [57]. Other alternative explanations must first be refuted before causality can be concluded [58].

Firstly, the virus could be an "innocent bystander" which is more prevalent in patients with ALRI, but has no causal role. Such an effect may be observed due to immunocompromised status from the true causal infection, or nosocomial infections. Secondly, the virus may be a risk factor for ALRI development, but not itself the primary cause. It has been well established that viral infections predispose to subsequent bacterial infection, although the exact mechanisms are still debated [59,60]. Indeed, influenza and RSV epidemics are commonly observed to precede those of bacterial pneumonia [61–63]. Thirdly, the virus may be necessary to cause ALRI, but is not sufficient to do so without the concurrent presence of one or more other causal factors. There are numerous risk factors that have been associated with ALRI, both host and environment [50]. Furthermore, there has been lethal synergism observed in viral–bacterial superinfections [64,65]. These, singularly or in combination, may provide the opportunity for the respiratory virus to cause ALRI. Fourthly, the virus may be the direct and sole cause of ALRI, with causality yet to be confirmed. Finally, the virus may be the joint cause of ALRI along with other concurrent viral respiratory infections.

Another essential criterion required for the determination of causality is establishment of the temporal sequence of exposure and outcome [57]. As exposure is investigated after the outcome in case–control studies, these cannot provide this evidence. Therefore, there is a rationale for the conduct of birth cohort studies with routine surveillance of children to track the circulation and course of respiratory viral infections. "Vaccine–probe studies" could be used to gain experimental evidence of each virus as a causal pathogen [66], although this is limited by vaccine availability of effective vaccines. These would allow conclusive assessment of the burden of ALRI attributable to each virus. Considerations of the causal role of these viruses are further complicated by the fact that a recent respiratory virus infection may have caused temporary immune–suppression leading to a subsequent viral or bacterial infection even though the initial infection can no longer be detected. Influenza viral infections leading to subsequent pneumococcal or staphylococcal respiratory infections have been well described [67]. This may result in an under–estimation of the burden of disease associated with respiratory viral infection.

Notwithstanding these limitations, this review provides clear evidence in favour of the causal role of RSV, IFV, PIV, MPV and to a lesser extent RV in childhood ALRI and presents first estimate of the proportion of ALRI cases that can be attributed to the viral exposure. Aetiological studies which simply report rates of viral identification as causal should make attempt to interpret findings in terms of the proportion of ALRI cases among children in whom a respiratory virus is identified that can be attributed to this viral exposure.

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Prevalence of rheumatoid arthritis in low– and middle–income countries: A systematic review and analysis

Igor Rudan[1*], Simrita Sidhu[1*],
Angeliki Papana[2], Shi–Jiao Meng[3],
Yu Xin–Wei[3], Wei Wang[3,4], Ruth M.
Campbell–Page[5], Alessandro Rhyll
Demaio[6,7], Harish Nair[1], Devi Sridhar[1],
Evropi Theodoratou[1], Ben Dowman[1],
Davies Adeloye[1], Azeem Majeed[8],
Josip Car[8,9], Harry Campbell[1], Wei
Wang [3,10], Kit Yee Chan[1,11]; Global
Health Epidemiology Reference
Group (GHERG)

[*] Joint first authorship

[1] The University of Edinburgh Medical School,
   Edinburgh, Scotland, UK

[2] University of Macedonia, Thessaloniki, Greece

[3] School of Public Health, Capital Medical
   University, Beijing, China

[4] Department of Integrated Early Childhood and
   Development, Capital Institute of Paediatrics,
   Beijing, China

[5] The University of Toronto, Toronto, Canada

[6] Copenhagen School of Global Health,
   University of Copenhagen, Denmark

[7] Harvard Global Equity Initiative, Harvard
   Medical School, Cambridge, USA

[8] School of Public Health, Imperial College
   London, London, UK

[9] Lee Kong Chian School of Medicine, Nanyang
   Technological University, Singapore

[10] Edith Cowan University, Perth, Australia

[11] School of Public Health, Peking University
   Health Science Centre, Beijing, China

Correspondence to:

Dr Kit Yee Chan
Centre for Population Health Sciences
The University of Edinburgh Medical School
Teviot Place, Edinburgh EH8 9AG
Scotland, UK
kchan16@gmail.com

Background Rheumatoid arthritis (RA) is an autoimmune disorder that affects the small joints of the body. It is one of the leading causes of chronic morbidity in high–income countries, but little is known about the burden of this disease in low– and middle–income countries (LMIC).

Methods The aim of this study was to estimate the prevalence of RA in six of the World Health Organization's (WHO) regions that harbour LMIC by identifying all relevant studies in those regions. To accomplish this aim various bibliographic databases were searched: PubMed, EMBASE, Global Health, LILACS and the Chinese databases CNKI and WanFang. Studies were selected based on pre–defined inclusion criteria, including a definition of RA based on the 1987 revision of the American College of Rheumatology (ACR) definition.

Results Meta–estimates of regional RA prevalence rates for countries of low or middle income were 0.40% (95% CI: 0.23–0.57%) for Southeast Asian, 0.37% (95% CI: 0.23–0.51%) for Eastern Mediterranean, 0.62% (95% CI: 0.47–0.77%) for European, 1.25% (95% CI: 0.64–1.86%) for American and 0.42% (95% CI: 0.30–0.53%) for Western Pacific regions. A formal meta–analysis could not be performed for the sub–Saharan African region due to limited data. Male prevalence of RA in LMIC was 0.16% (95% CI: 0.11–0.20%) while the prevalence in women reached 0.75% (95% CI: 0.60–0.90%). This difference between males and females was statistically significant ($P < 0.0001$). The prevalence of RA did not differ significantly between urban and rural settings ($P = 0.353$). These prevalence estimates represent 2.60 (95% CI: 1.85–3.34%) million male sufferers and 12.21 (95% CI: 9.78–14.67%) million female sufferers in LMIC in the year 2000, and 3.16 (95% CI: 2.25–4.05%) million affected males and 14.87 (95% CI: 11.91–17.86%) million affected females in LMIC in the year 2010.

Conclusion Given that majority of the world's population resides in LMIC, the number of affected people is substantial, with a projection to increase in the coming years. Therefore, policy makers and health–care providers need to plan to address a significant disease burden both socially and economically.

In recent years there has been a shift in diseases and health related challenges that the world is facing. Non–communicable diseases (NCD) have emerged as the leading cause of death worldwide, accounting for two–thirds of all deaths and deaths are projected to increase in the coming years [1]. Contrary to popular belief, these diseases are not limited to the developed world; they are increasingly prevalent in low– and middle–income countries (LMIC), which are facing the double burden of both communicable and non–communicable diseases [2]. In LMIC, constrained health care facilities, lack of resources and funds at individual and national level lead to limited treatment and support for NCD, which mainly affect the working age population with a negative impact on household incomes and equity. The high burden of NCD poses additional problems for LMIC, creating a vicious cycle by worsening poverty that in turn results in a further rise of NCD [1]. Acknowledgment of the serious implications of the global burden of NCD has led to an international response. The United Nations (UN) High–level meeting on NCD in 2011 addressed these issues and has paved the way for tackling them, by providing guidance on how to strengthen national capacities to address NCD and integrate prevention and control activities across sectors and at all levels of governance and health–care provision in LMIC [1,2].

While there is wide recognition of the four main NCD with a major contribution to the global burden – cardiovascular diseases, cancers, diabetes mellitus and chronic respiratory illnesses [2] – there are a large number of other NCD that cause extensive morbidity, but are neglected as they do not significantly contribute to mortality. One such disease is rheumatoid arthritis (RA), the most common type of inflammatory musculoskeletal disorder [3,4], in which the quality of life has been reported to be lower than in patients suffering from most of the other NCD [5,6]. It is a chronic systematic autoimmune inflammatory disease, characterised by a symmetrical persistent synovitis of the joints of the hands, wrist, feet and knee resulting in tender swelling of joints, pain, limitation in motion and morning stiffness. Its systematic features include fatigue, generalised weakness, loss of weight and low grade fever [7]. As the disease advances, irreversible tissue damage occurs, with destruction of bone and cartilage leading to joint deformity, muscle atrophy, and progression that may involve all joints of the body [8]. For the purpose of clinical trials, RA is diagnosed using the American College of Rheumatology (ACR) criteria, formerly known as the American Rheumatology Association (ARA) criteria [7,9].

The prevalence of RA in the western world is 1–2% [10], and is believed to be 1% worldwide [11]. However, this global estimate is based on a few sporadic studies over different time periods, in a limited number of LMIC. Extrapolation from a few studies is problematic given that there is ample evidence that RA is a variable disease in time and place [11]. Moreover, the burden of NCD has increased over the past decade in LMIC, while it has decreased in high–income countries [11]. RA also has a substantial economic impact, which can be quantified as direct (cost of medication, hospital stay and visits, care–givers and helpers); indirect (loss of productivity from absenteeism or early retirement); and intangible costs that are measured by the impact on quality of life [12,13]. In the United States, the direct cost of RA was approximately US$ 13 500 per affected person per year, and indirect costs could range between US$ 1000 and US$ 33 000 per affected person per year [14]. However, not much is known about costs in the developing world [13].

This paper aims to provide an estimate for the global and regional burden of rheumatoid arthritis by systematically reviewing relevant literature in both English databases and those in other languages; to study the variation in the prevalence of rheumatoid arthritis by gender, region and setting (urban/rural); and to discuss the significance of these prevalence estimates and their implications for public health policy.

METHODS

Definition of population under study and literature search

The World Bank database was referenced to compile a list of all the LMIC in the world [15]. Thereafter, all LMIC were grouped into regions in accordance to the World Health Organization (WHO) regions [16]. WHO divides the world into six regions; Southeast Asian Region (SEAR), Eastern Mediterranean Region (EMR), Western Pacific Region (WPR), Europe (EUR), The Americas (AMR) and Sub–Saharan Africa (AFR) [17–19]. A systematic literature search was conducted separately for each region to find population based studies that documented the prevalence of RA. Medline (1946 – July week 1, 2013), EMBASE (1976–2013 week 26) and Global Health (GH) (1973 – 2013 week 26) were searched using the OVID search engine (search terms available in **Online Supplementary Document**). Both Medical Subject Headings (MeSH terms) and keywords were used in OVID. Other online databases such as PubMed, Web of Knowledge (WoK) and databases selective to regions, such as LILACS for Latin America, CNKI and Wan Fang for China, and IndMed for India, were also thoroughly searched. PubMed was searched for all regions, as it proved to be broader and more sensitive in picking up studies. Grey literature was also searched for all low–middle income countries using SIGLE (OpenGrey), Google Scholar and Global Health library. The search of grey literature resulted in 10 and 149 studies, respectively, none of which were relevant to this analysis.

Inclusion and exclusion criteria for study selection

After the initial screen, inclusion and exclusion criteria were applied to retain only the studies that were free of any apparent bias. We included studies conducted in LMIC from all WHO regions that were population based or community based, studies conducted after 1987 that used ARA/ACR diagnostic criteria (see **Table 1**), focused on adult populations (typically 15+ or 18+ years, with exclusion of juvenile forms in the former studies) and reported the prevalence rate of RA. We excluded review articles with secondary data only (with the exception of sub–Saharan Africa, where the amount of data was particularly scarce), hospital–based studies (for lack of representativeness of the general population), studies conducted prior to or during 1987 (for inconsistent case definition), studies on other types of arthritis in adults, studies on juvenile forms of arthritis and studies that used other diagnostic criteria to measure the prevalence of RA in the population.

We retained studies that clearly presented the method of diagnosing RA, beginning with how the sample population was recruited and evaluated, along with the criteria used for diagnosis of RA. We expected that trained personnel or specialists be involved in the field work, and we excluded the studies where self–reporting was the primary method of case ascertainment. Specialists (doctors, rheumatologists) needed to be involved in the next step of confirmation. Any study where there was no direct contact between the assessors and sample population, such as telephone surveys, were excluded. There is a high probability of misclassification and oversight of cases by untrained or inadequately trained personnel, or through indirect contact.

Figure 1 summarises the process of study selection for all six WHO regions. First, duplicates were excluded and titles and abstracts of the retained papers were evaluated for rel-

evant studies. Full texts of selected studies were analysed and inclusion and exclusion criteria were applied. Data from all relevant studies was extracted into an Excel spreadsheet, where sample size (age, sex–specific, mean age), methodology, criteria used for diagnosing RA, study location (urban or rural) and prevalence rate were documented for each study.

Adjustment of prevalence rates

Once the final set of studies was retained (**Figure 1**), crude prevalence rates, sex–specific prevalence rates, urban and rural prevalence rates and male–to–female ratio of RA cases were adjusted to the same measurement unit and expressed as a percentage. Data extracted from each study is shown in the **Online Supplementary Document**. Checks for internal consistency of the data were made and possible significant correlations between prevalence rate and the sample size, year of publication of the study, sex and residency were made.

Statistical analyses

All statistical analyses are shown in the **Online Supplementary Document**. We first tested the distribution of the reported prevalence of RA across all identified studies for normality using the one–sample Kolmogorov-Smirnov test. We concluded that the results did not indicate normal distribution, presumably because of substantial heterogeneity in the included studies ($Z = 1.831$, $P = 0.002$). We then performed a meta–analysis of all identified studies in all LMIC using the DerSimonian–Laird method, to determine the "LMIC" prevalence rate (**Online Supplementary Document**).

We then displayed mean and median prevalences in each of the six WHO regions (**Figure 2**). The Kruskal-Wallis

Table 1. The criteria of the American College of Rheumatology (ACR) established in 1987 to assist clinical diagnosis of rheumatoid arthritis*

1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joints	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta–articular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on postero–anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify

PIP – proximal interphalangeal; MCP – metacarpophalangeal; MTP – metatarsophalangeal

*Four out of the seven criteria need to be met in order to establish the diagnosis of RA, with criteria 1–4 required to be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded [9].
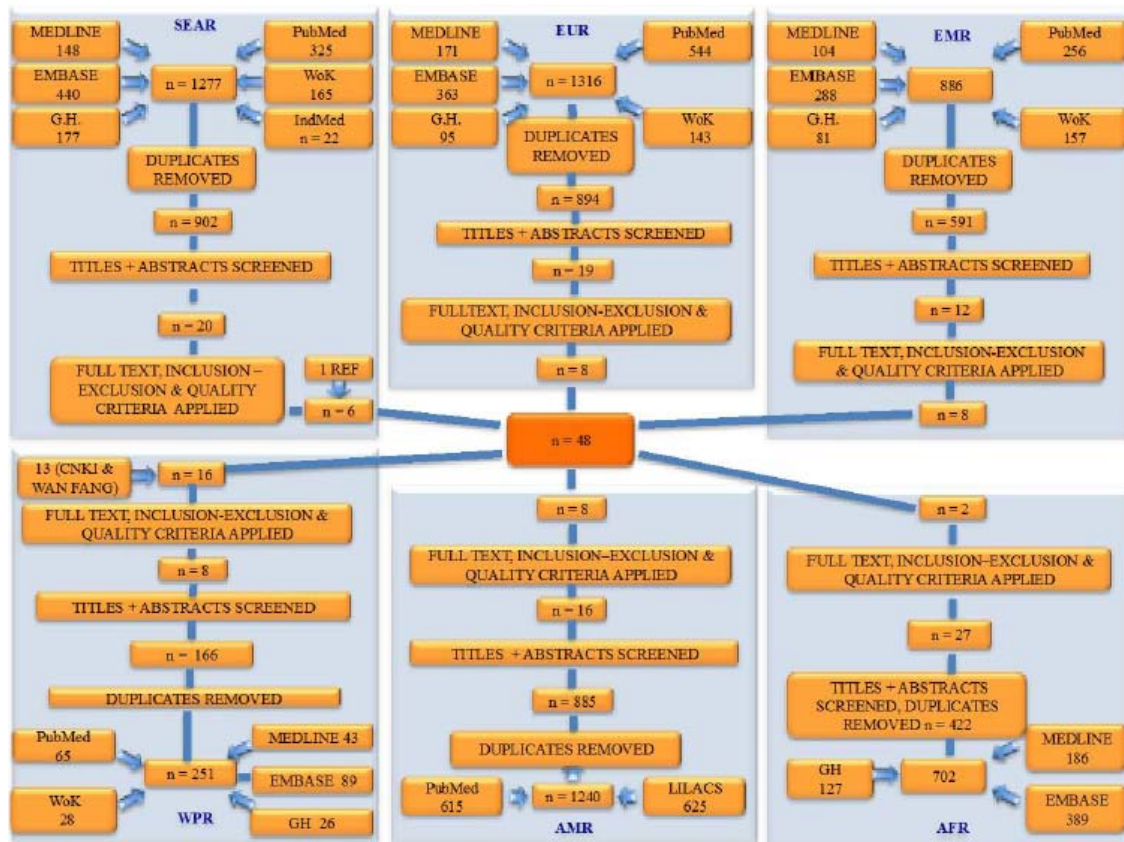
Figure 1. Flowchart presenting the literature search and the process of study selection (WoK = Web of Knowledge; G.H. = global health).
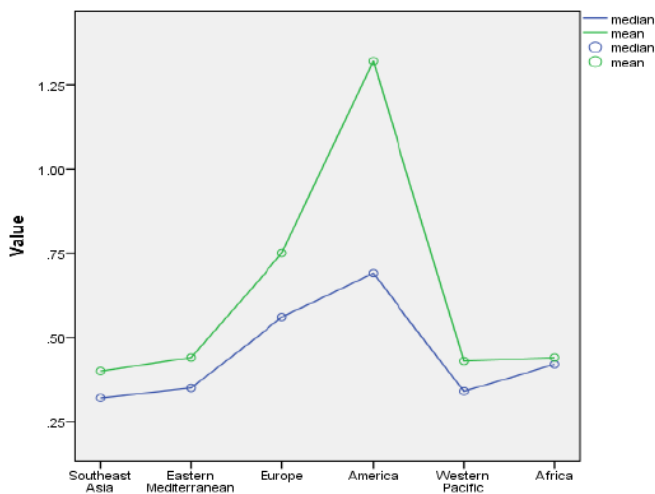
Figure 2. The relationship between mean and median prevalence of rheumatoid arthritis in low and middle–income countries in six WHO regions of the world.

one–way analysis of variance by ranks examined whether samples originated from the same distribution. After this, we conducted a series of region–specific meta–analyses to estimate regional prevalence and confidence intervals, using the DerSimonian–Laird method (**Online Supplementary Document**).

An important possible confounding effect was differences in the mean age of the sample between the studies. This is because, although all samples were defined as "adult population" (usually 15 years of age or older), the relative contribution of elderly population varied in different countries because of difference in sampling strategies and overall life expectancy. We explored the association between the prevalence of RA and the mean age using linear correlation coefficients (Pearson, Kendall's tau, and Spearman), and also the generalised dependence measure mutual information to exclude the potential effect of age distribution on generalisability of the results (**Online Supplementary Document**).

Association between gender and prevalence of RA, where a considerable difference between sexes was expected, was explored using the paired samples t–test. We then conducted a gender–specific meta–analysis to estimate prevalence and confidence intervals in men and women, using the DerSimonian–Laird method. In addition, box–and–whiskers plots of regional prevalence by gender were also presented (**Online Supplementary Document**). We also examined the difference in prevalence of RA between urban and rural populations. Since the RA prevalence is not normally distributed, we performed the non–parametric Mann-Whitney U test to test the null–hypothesis.

RESULTS

In our study, the majority of studies were from mainland China, with additional studies from Taiwan and Hong Kong. Mexico, Turkey, Iran, India, Pakistan, Philippines and Russia were also represented through multiple studies. The median year of publication was 2004, making the estimate useful for application to both the world population in 2000 and 2010. Twenty–one studies used the ARA criteria, and all the remaining studies used the 1987 revised ACR criteria. Some studies had multiple cohorts. Each cohort was recognised separately during analysis, so that the final 48 studies resulted in 60 cohorts. In case of the African region, only two studies were found from the entire region that fulfilled the criteria for inclusion. One of the studies had a very small sample size and did not find a single case of RA, so it was excluded as uninformative. The other study had a crude prevalence rate of 1%, but we felt that it would be inadequate to base an entire regions' prevalence rate on a single study. Therefore, we decided to discard both of those studies and replace them by Bowman's systematic analysis in 2012 [20]. Bowman included all the studies ever conducted in Africa in his estimate, irrespective of the year of study, and the prevalence rate from his study was then applied to the population statistics of the region in 2000 and 2010.

When all studies were analysed in one large meta–analysis, irrespective of their heterogeneity, this resulted in an "LMIC" estimate for the prevalence of RA of 0.53% (95% CI: 0.45–0.61%). Analysis of heterogeneity confirmed that the data were highly heterogeneous ($I^2 = 96$%) (**Online Supplementary Document**). We then studied the mean and median prevalence in each of the six WHO regions (**Figure 2**) and presented box–and–whiskers plot of the results from studies in each region (**Figure 3**). The Kruskal-Wallis one–way analysis of variance by ranks test showed that the prevalence in at least one of the WHO regions was statistically different from the others ($P = 0.029$).

A series of region–specific meta–analyses were conducted to estimate regional prevalence of RA. The meta–analysis estimates of regional RA prevalence rates were 0.40% (95% CI: 0.23–0.57%) for Southeast Asia, 0.37% (95% CI: 0.23–0.51%) for Eastern Mediterranean, 0.62% (95% CI: 0.47–0.77%) for European LMIC countries, 1.25% (95% CI: 0.64–1.86%) for American LMIC countries and 0.42% (95% CI: 0.30–0.53%) for Western Pacific LMIC countries, respectively. This analysis could not be performed for Africa due to limited data. The data sets were heterogeneous in all the regions (I^2 varied from 74.2% to 97.3%).

We then studied whether the mean age of the sample contributed to the observed prevalence rates. Linear correlation coefficients (Pearson, Kendall's tau, and Spearman)
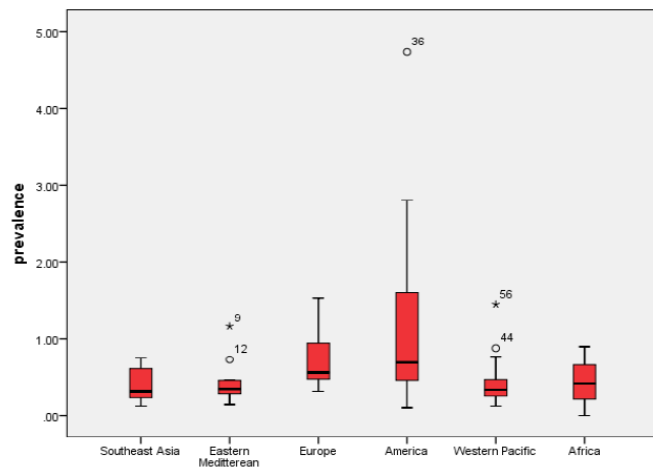
Figure 3. Regional median, minimum and maximum observed value and inter–quartile range for the prevalence of rheumatoid arthritis in low and middle–income countries in six WHO regions of the world.

and the generalised dependence measure mutual information did not show an effect of mean age of the sample on the reported prevalence of RA across the studies ($P = 0.0599$; $P > 0.05$), implying that the differences in age structure of samples in different studies were not the main determinant of the observed heterogeneity.

An investigation into differences in prevalence by gender using paired samples t–test indicated that the male and female RA prevalence differed significantly ($P < 0.0001$), which was expected. We therefore conducted a separate meta–analysis of the RA prevalence in LMIC countries for men and women. Male prevalence was 0.16% (95% CI: 0.11–0.20%) (**Figure 4**) while the prevalence in women was five times higher, amounting to 0.75% (95% CI: 0.60–0.90%) (**Figure 5**). Data seemed to be less heterogeneous for men ($I^2 = 49.6$%) than for women ($I^2 = 83.7$%).

We also examined the difference in prevalence of RA between urban and rural populations, wherever information was available to allow for comparison. Since we established that the RA prevalence was not normally distributed, we performed the non–parametric Mann-Whitney U test to test the null hypothesis. The significance of the test was $P = 0.353$, indicating that the prevalence in the urban and rural settings do not differ significantly (**Figure 6**).

After all the previous analyses, a strategy was needed for estimating the number of persons living with RA in LMIC in the years 2000 and 2010. Possible approaches were: (i) to apply the meta–analysis of the crude prevalence from all identified studies to the total number of persons 15 years or older in LMIC; (ii) to use the estimate of prevalence for males and for females that resulted from the meta–analyses of all studies that reported the rates separately by gender;
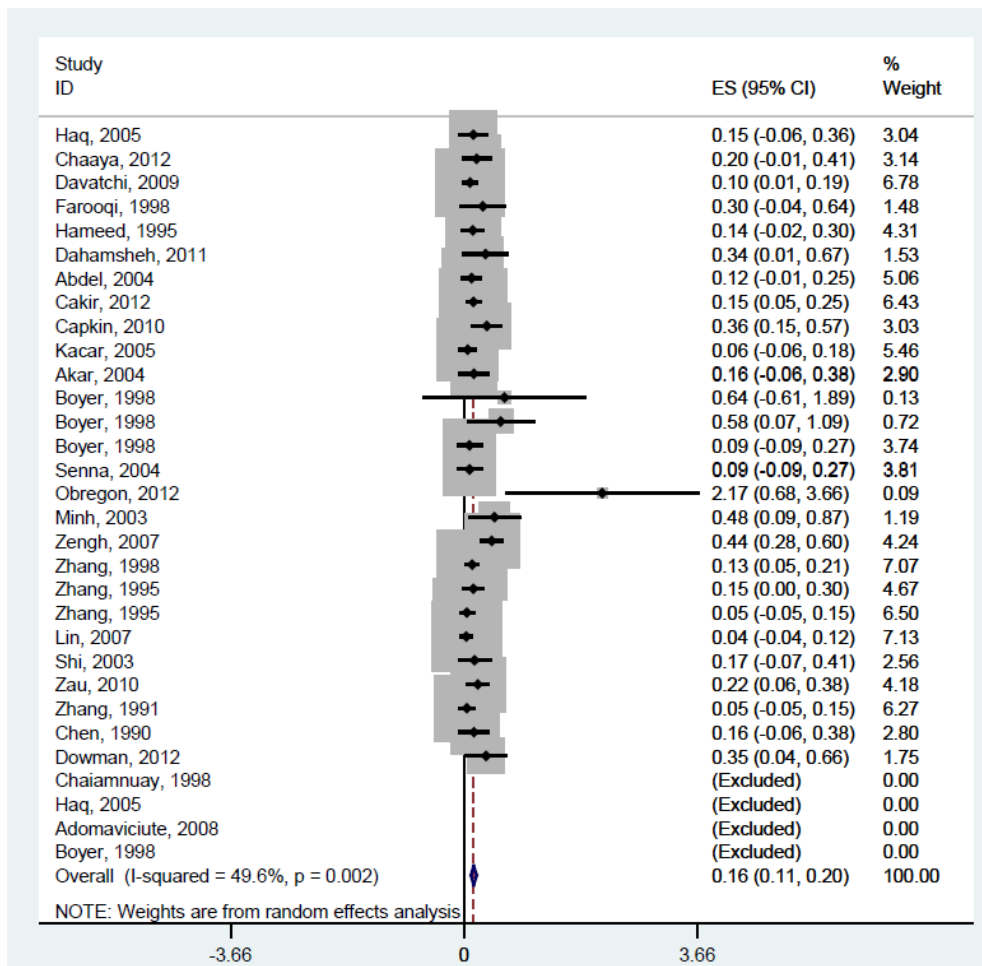
Figure 4. Meta–analysis of rheumatoid arthritis prevalence in men, based on all available information from low and middle–income countries in six WHO regions of the world.

then, to apply those two estimates of prevalence to male and female populations in LMIC; (iii) to use regional medians or the estimates based on regional meta–analysis and apply them to the regional populations aged 15 years or older; (iv) finally, to use sex–specific regional estimates and apply it to male and female population aged 15 years or older in respective regions.

Given the quantity and quality of the information that was obtained through this systematic review, the most appropriate (and robust) approach was to use gender–specific estimates of prevalence for the whole LMIC region and apply them to male and female populations in LMIC. There are a number of reasons why other approaches were not preferred and we will list them here. Although the quantity of information was the largest for the approach (i) above, there is uncertainty in some studies over the composition of sample by gender, and whether it is representative of the underlying population. Given that gender is an extremely important determinant of prevalence, the approach (i) would suffer from a possible confounding effect of the gender composition of the sample. The strength of approach (iii) was that it could account for regional varia-

tion. However, the number of studies typically available for different regions was simply too small to be sure whether the observed differences between regions were real, or just stochastic. The same applies to approach (iv). Therefore, approach (ii) was used, because it accounted for the most important confounding variable – gender – and because it provided a lot of information for meta–analysis in each gender. This allowed an assumption that the rates considered representative for all males and all females in LMIC were more likely to be accurate than region–specific rates. Moreover, the observed heterogeneity of the underlying data was the lowest in gender–specific meta–analysis across LMIC.

This gives an estimate of male prevalence of 0.156% (95% CI: 0.11–0.20%) (**Figure 4**) that needs to be applied to the male population aged 15 years or more in LMIC in 2000 and 2010. In females, the prevalence of 0.747% (95% CI: 0.60–0.90%) is used (**Figure 5**). The UN Population Division's estimates for the number of males aged 15 years or older in LMIC in the year 2000 is 1.667 billion, and in the year 2010 it is 2.206 billion [17]. For women, the corresponding figures are 1.634 billion for the year 2000 and 1.991 billion in 2010 [17]. This translates into 2.60 (95% CI: 1.85–3.34%)
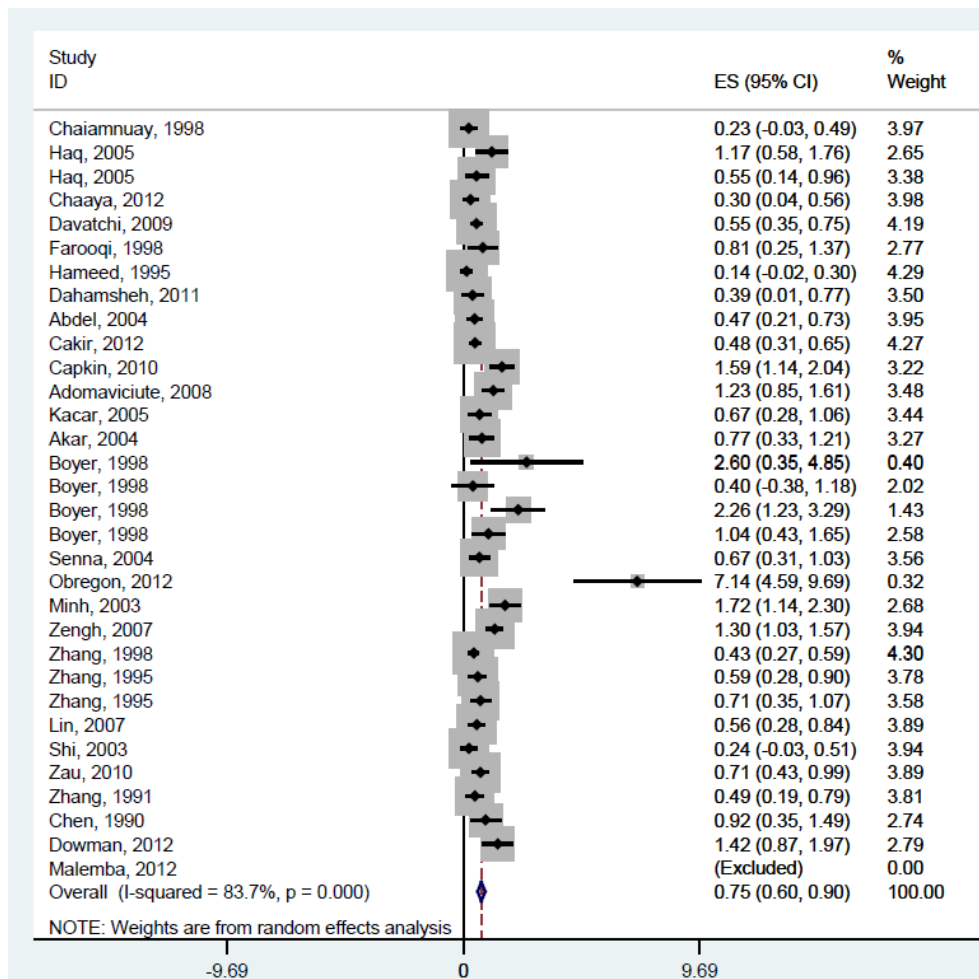
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Figure 5. Meta–analysis of rheumatoid arthritis prevalence in women, based on all available information from low and middle–income countries in six WHO regions of the world.
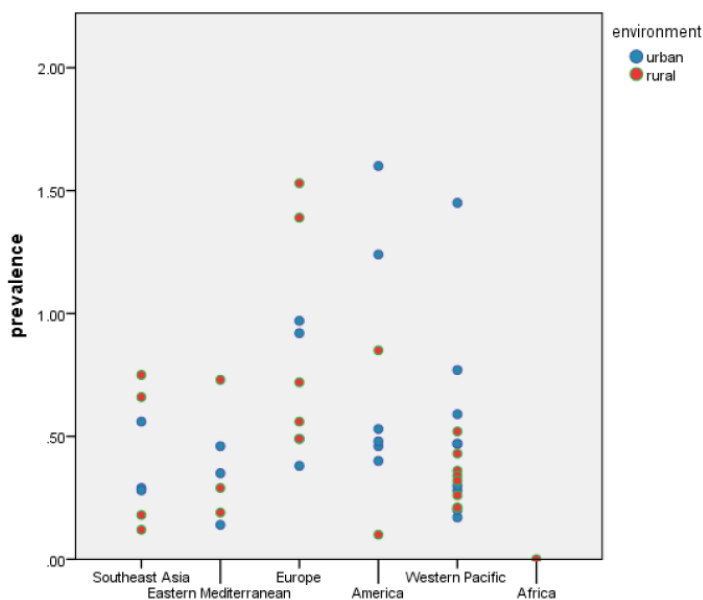
Figure 6. A scatterplot of observed prevalence rates of rheumatoid arthritis in six WHO regions based on urban or rural residency of the examinees. No statistical differences were noted (see **Online Supplementary Document** for further detail).

million male sufferers and 12.21 (95% CI: 9.78–14.67%) million female sufferers in the year 2000, and 3.16 (95% CI: 2.25–4.05%) million affected males and 14.87 (95% CI: 11.91–17.86%) million affected females in the year 2010 in the countries of low and middle income.

DISCUSSION

We presented a robust estimate of the number of individuals suffering from RA in low and middle income countries in 2000 and 2010. There have already been several attempts to estimate the prevalence of RA at the global, regional and national level and also in LMIC [10,11,14,18,19]. In comparison to previous estimates that presented both higher and lower estimates than our study, our estimate is based primarily on a substantial amount of evidence from LMIC on sex–specific prevalence. We demonstrated that gender is a principal determinant of RA in LMIC and that age distribution of the population and being an urban dweller do not contribute significantly to disease development. This is different from some other diseases, such as dementia and cancer, where age seems to be the main de-

terminant, or schizophrenia, where being an urban dweller and family history seem to be the main driver of the disease occurrence [1,2]. Therefore, we believe that our strategy for deriving the estimate was more appropriate than used in some previous studies. Moreover, we provide the full data set used to develop the estimates in **Online Supplementary Document** and all our methods are transparent and replicable by other groups.

Still, there are limitations in all estimates of the current global burden of RA. The criteria of defining the disease have changed over time and the estimates that don't take this into account will be internally inconsistent. Moreover, a mixture of studies, both hospital and population based studies, could be considered, although the former will present the more severe end of disease spectrum and bias the results. A major strength of our study is that it made use of all literature available in all languages, including two major Chinese databases and the database with grey literature. We therefore believe that we are presenting the most advanced estimate of RA burden to date. However, limitations are still large: there are very few data points (particularly in Africa) and most LMIC countries do not have a single published epidemiological study. Moreover, most of the studies used for this estimate are quite small and they are unlikely to be nationally representative. Also, this study uses a wide range of years to provide estimates for 2000 and 2010, which is a limitation given that prevalence may be changing over time and that the time trend reported here arises from demographic changes, rather than our understanding of the epidemiological situation.

Our paper also aimed to explore whether other major covariates, besides gender, affect the frequency of the occurrence of RA. We were unable to demonstrate significant effects for either urban / rural living or age structure of the study sample. Comparing all urban, rural and mixed studies amongst each other, we were unable to demonstrate significant differences between prevalence rates in urban or rural areas. This is contrary to some previous reports that suggested that the prevalence might be higher in urban areas [21]. Moreover, previous reports suggested that the prevalence rate in LMIC is lower than in the developed countries [22], which our study seems to generally support.

One of the major strengths of our study is that it involved a systematic search of ten large databases, resulting in the identification of 10 599 studies initially and 48 studies selected for inclusion. Native speakers translated studies in a language other than English, specifically Chinese and Spanish. This has greatly increased the pool of studies available for analysis, as it led to the inclusion of studies otherwise excluded due to language barriers. All of the studies used the same definition to identify RA in patients: the 1987 revised ACR criteria (previously known as ARA criteria). This enabled comparison and convergence of stud-

ies towards a single plausible estimate. Besides three studies, in which we adjusted the estimate, all others determined the prevalence rate using the same age cut–off (15 years or older), again leading to comparable estimates underlying each regional and the overall prevalence rate.

Although the best quality of epidemiological work on RA in LMIC has been conducted by WHO–ILAR–COPCORD [23], this program covers a limited number of countries and this current review includes a larger number of studies conducted elsewhere, by different researchers, leading to wider coverage. Still, nearly all of the retained studies closely followed the three–step methodology set by WHO–ILAR–COPCORD and used similar questionnaires, thereby decreasing the methodological variability in the studies [23]. The questionnaires were translated in local languages and tested before the start of the studies in almost all cases.

Nevertheless, variation remained even within the selected studies that share the same three–step methodology. The assessors at each stage were different between the studies. In some studies, trained nurses administered the questionnaire, while in others this was done by trained volunteers and students. At the second and third stage most studies involved rheumatologists, but a handful of studies had general medical doctors or internists evaluate the potential cases. Moreover, among the studies conducted by COPCORD, there was a slight regional variation in the questionnaire used, given that it was modified over time, decreasing the comparability of studies. Although the number of participants at each step is given, the reason of non–participation is not stated in all studies. This may have led to non–respondent bias. Although this problem cannot be easily controlled, it still needs to be acknowledged, as there may be a difference in characteristics of those who participate and those who do not.

Research in developed countries does not seem to suggest a growing trend in the prevalence of the disease. However, the total number of cases grew considerably between 2000 and 2010 because the population of LMIC older than 15 years has grown in this period [24]. Even a slight increase in the prevalence rate, eg, an additional prevalence of 0.1%, would translate to an increment of 4 million affected persons. Given the fact that RA affects the working age population and most of the employment in these countries is still for manual labour, it greatly decreases the productivity of countries as a whole [25]. Additionally, the high costs of treatment, borne by individuals themselves in the most LMIC, counters other efforts to decrease poverty and improve living standards.

As RA is an important condition with significant morbidity and economic impact, it should be at the forefront in health care policy. Despite this, RA as part of a larger group of NCD receives less than 3% of annual development assistance for health to low and middle income countries.
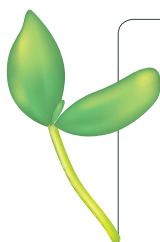
The neglect of NCD on the global stage can be explained not only by the gaps in estimates on burden of disease but also from a lack of strategic communication about the urgency of the problem [26].

In this paper, estimates of RA morbidity aim to take a first step in raising awareness of policy makers and health care workers, as previously they have had to rely on the evidence that was generated mainly in the developed world. The lack of specialists to diagnose and treat this condition should also be addressed. In certain African nations there is only one rheumatologist for the entire population [21]. Therefore, an increase in the number of specialists in this area is urgently needed in LMIC [27]. As this takes time, the existing doctors in the community should be offered specific education on RA, including newer treatment regimens and the management of the associated comorbid conditions. As most of the population resides in rural areas, incorporating identification and treatment of the disease in community health care system is crucial to reach all those in need of diagnosis and treatment. Funding should be targeted at increasing efficacy of treatments in LMIC. Efforts should be made to increase the availability of treatment – both anti–inflammatories and the newer biological agents that have proven to be greatly beneficial – at affordable costs. The newer biological agents are very expensive and it is unlikely that many LMIC could afford to supply them [25]. Moreover, RA is associated with an increased risk of other diseases (such as cardiovascular diseases) and the management of these comorbid conditions is also important. All doctors should be made aware of treatment protocols already in use by high–income countries with emphasis on early treatment, to slow disease progression and elimination of pain. This should lead to improvements in quality of life and decrease the occurrence of co–morbid conditions, such as depression. The set–up of supportive treatment, such as physiotherapy, should be encouraged [11–18].

Infrastructure for research in areas where it is currently unavailable should be set up. Allegiance with international agencies already working towards generating information, such as WHO–ILAR [23], should be undertaken and their efforts should be supported. In Africa, the African League of Associations of Rheumatology (AFLAR) already exists, but little has been done in terms of research and surveillance of rheumatologic diseases [20]. Such associations should be supported, encouraged and pressurised by governments to carry on more work in this area. The WHO–ILAR–COPCORD program was developed to identify all types of musculoskeletal disorders, and not specifically designed for rheumatoid arthritis nor as an epidemiological study program [23]. Therefore, further research should be specifically orientated towards rheumatoid arthritis, with greater attention on the methodology. The lack of information from more than 100 LMIC countries should be addressed and gaps filled. Studies should also include age groups of those with the disorder, thereby providing more information on who bears the greatest burden and allowing age–standardised comparison. Simultaneously, information about risk factors should be obtained and incorporated in study designs.

The estimates presented in this paper provide a building block for future epidemiological studies by suggesting the way forward in disease assessment in LMIC context and the methodology that could be deployed. It could also be used to create awareness among health–care workers and education of people about the disease and encourage health–seeking behaviour for provision of available treatment, which can decrease the burden associated with disability and bring about a decrease in morbidity. It is also noteworthy to point out the reoccurring theme of lack of data from the poorest countries. Policy makers from these countries should show more dedication and step up their efforts towards research in the health care sector, as generating information about the burden of disease is the first step in decreasing its prevalence.

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Prevalence of schizophrenia in China between 1990 and 2010

PAPERS

Kit Yee Chan[1,2,3*], Fei–fei Zhao[4*], Shijiao Meng[4,*], Alessandro R Demaio[5,6], Craig Reed[1,2], Evropi Theodoratou[1,2], Harry Campbell[1,2], Wei Wang[4**], Igor Rudan[1,2**]; Global Health Epidemiology Reference Group (GHERG)

*Joint first authors
**Joint senior authors

[1] Centre for Global Health Research and Global Health Academy, University of Edinburgh Medical School, Scotland, UK

[2] World Health Organization's Collaborative Centre for Population Health Research and Training

[3] Nossal Institute for Global Health, University of Melbourne, Australia

[4] Municipal Key Laboratory of Clinical Epidemiology, School of Public Health, Capital Medical University, Beijing, China

[5] Harvard Global Equity Initiative, Harvard Medical School, Boston, USA

[6] Copenhagen School of Global Health, University of Copenhagen, Denmark

[7] School of Medical Sciences, Edith Cowan University, Perth, Australia

Background Economic development and changes in lifestyle in many low and middle–income countries (LMIC) over the past three decades may have affected mental health of their populations. Being the most populous country and having the most striking record of development, industrialization and urbanization, China provides an important opportunity for studying the nature and magnitude of possible effects.

Methods We reviewed CNKI, WanFang and PubMed databases for epidemiological studies of schizophrenia in mainland China published between 1990 and 2010. We identified 42 studies that reported schizophrenia prevalence using internationally recognized diagnostic criteria, with breakdown by rural and urban residency. The analysis involved a total of 2 284 957 persons, with 10 506 diagnosed with schizophrenia. Bayesian methods were used to estimate the probability of case of schizophrenia ("prevalence") by type of residency in different years.

Findings In urban China, lifetime prevalence was 0.39% (0.37–0.41%) in 1990, 0.57% (0.55–0.59%) in 2000 and 0.83% (0.75–0.91%) in 2010. In rural areas, the corresponding rates were 0.37% (0.34–0.40%), 0.43% (0.42–0.44%) and 0.50% (0.47–0.53%). In 1990 there were 3.09 (2.87–3.32) million people in China affected with schizophrenia during their lifetime. The number of cases rose to 7.16 (6.57–7.75) million in 2010, a 132% increase, while the total population increased by 18%. The contribution of cases from urban areas to the overall burden increased from 27% in 1990 to 62% in 2010.

Conclusions The prevalence of schizophrenia in China has more than doubled between 1990 and 2010, with rates being particularly high in the most developed areas of modern China. This has broad implications, as the ongoing development in LMIC countries may be increasing the global prevalence of schizophrenia.

Correspondence to:

Professor Igor Rudan
Centre for Global Health Research
The University of Edinburgh Medical School
Teviot Place
Edinburgh EH8 9AG
Scotland, UK
igor.rudan@ed.ac.uk

Schizophrenia is a complex psychiatric disorder associated with significant financial costs to patients and societies [1,2]. The etiology of schizophrenia is still not understood, but both genetic, environmental and behavioral risk factors have been proposed, as well as associations with greater levels of economic development, industrialization and urbanization [3,4]. Dramatic development and changes in lifestyle in many low and middle–

income countries (LMIC) over the past three decades may have affected mental health of their populations. Being the most populous country and having experienced rapid development and urbanization, China provides an important opportunity for studying the nature and magnitude of possible effects [4–12]. The mechanisms through which development and urbanization increase schizophrenia risk are not understood [5–7]. Several hypotheses have been proposed, but presently there is insufficient evidence in their support [6–9]. Exploring them further remains a significant challenge, which is particularly true in LMIC where the availability and quality of epidemiological information is often suboptimal [13].

Epidemiological and demographic evidence in China has improved over the past two decades and Chinese academic journals have become accessible in electronic databases such as China National Knowledge Infrastructure (CNKI) and Wanfang [14–18]. Demographic data imply that the proportion of Chinese population living in urban areas has increased from about one quarter to one half between 1990 and 2010 [18]. We may therefore expect a significant increase in both the prevalence and the absolute number of cases of schizophrenia in China over the past two decades, along with a growing population–attributable fraction assigned to development, industrialization and urbanicity. To explore this, we conducted a systematic review of the literature in Chinese and English to analyze trends in the prevalence of schizophrenia in China over the 20–year period from 1990 to 2010 in urban and rural regions. Any changes observed in China may also have relevance for many other LMIC with large rural–to–urban migration associated with industrialization.

METHODS

Literature search strategy and search terms

Systematic reviews of China National Knowledge Infrastructure (CNKI), Wanfang and PubMed were conducted for the publication years 1990 to 2010. Searches of the Chinese databases were performed independently by two co–authors (FFZ and SJM), and subsequent PubMed searches by two further co–authors (ARD and KYC). Table s1 in **Online Supplementary Document** shows the search terms for the Chinese databases, which consisted of the Chinese and English terms for schizophrenia searched in combination with each of the following: epi* (all Chinese terms for epidemiology), incidence (in two Chinese variants), cross–sectional study (in two Chinese variants), prevalence, point prevalence, mortality, case–fatality and attack rate. Based on the results of the detailed Chinese searches, the search terms for PubMed were reduced to "schizophrenia AND China AND (inciden* OR prevalence OR morbidity OR mortality)".

Inclusion and exclusion criteria

The two Chinese databases initially yielded a total of 8642 titles, while PubMed yielded 467. Papers were first excluded on the basis of duplicate publications within and between databases, studies with no numerical estimates, studies of Chinese population outside of mainland China, reviews, and viewpoints, reducing the yield to 122 full–text papers. Further studies were excluded if they reported less than 20 schizophrenia cases, had no clear denominator or were not representative of the general population. In reviewing the methods of each paper further exclusions were made on the basis that the paper did not provide a clear differentiation between rural and urban residents or had failed to specify whether the reported prevalence was lifetime or point prevalence. Finally, after checking the case definition used in each paper, only papers that had applied a 'gold standard' case definition were retained (ie, Diagnostic and Statistical Manual of Mental Disorders (DSM)–III or IV, International Classification of Diseases (ICD)–9 or 10, or Chinese Classification of Mental Disorders – CCMD–II and above). Four papers were excluded because they reported only incidence or mortality rates with no prevalence estimates. Direct contact was made with the corresponding authors of 13 of the retained studies to obtain missing information related to the inclusion criteria, thus removing any ambiguities about the studies. Publications from the same field site that reported partial results were merged and counted as one study. **Figure 1** shows the PRISMA (acronym for: preferred reporting items for systematic reviews and meta–analyses) diagram illustrating the process of selection of studies.

Geographic location and study year of the retained studies

After all exclusions, 42 prevalence studies were retained. Their full references are presented in Table s2 in **Online Supplementary Document**. The key characteristics of the studies are summarized in **Table 1**. The studies were mostly large population–based studies. They typically used a two–stage data collection design in which trained medical assessors performed an initial population–based screening in Phase 1 and psychiatrists performed a detailed evaluation in Phase 2 (see Table s3 in **Online Supplementary Document** for further explanation on study design, agreement statistics and validation of the estimates). We defined "year of study" as the median year of the exact period during which the study was conducted. Geographically, the retained studies covered 21 of mainland China's 31 provinces, municipalities and autonomous regions (Table s4 in **Online Supplementary Document**). Their geographic distribution is shown in **Figure 2.**
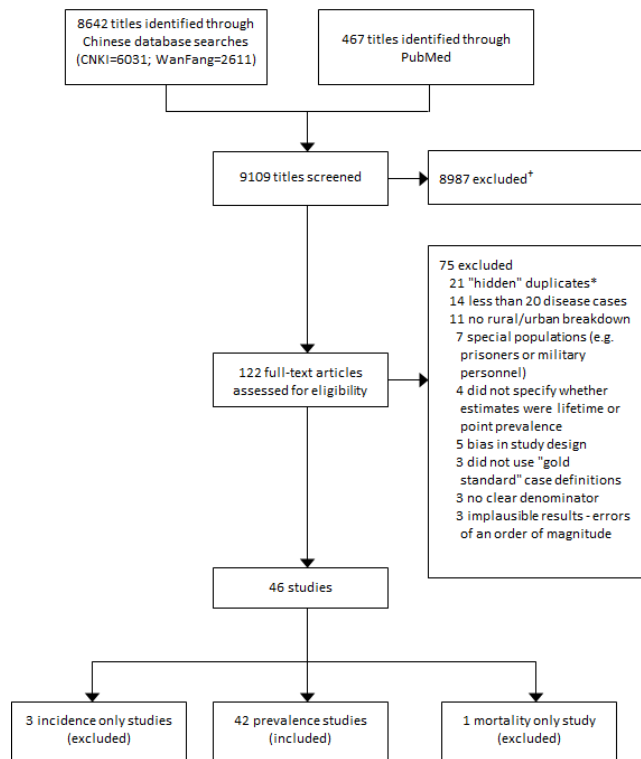
Figure 1. PRISMA diagram of study selection. †The large majority was excluded because they were duplicate returns of the same reference under different search terms or in different databases; the others were excluded because they were irrelevant to the topic of our study, provided no numerical estimates, or studied Chinese populations outside of mainland China. *These are reports of the same results in different journals.

Table 1. Characteristics of the cross–sectional studies

Study characteristics	Number of studies (n = 42)
Sample size (n):	
<5000	8 (19.0%)
5001–10 000	9 (21.4%)
10 001–20 000	11 (26.2%)
20 001–60 000	7 (16.7%)
>60 000	7 (16.7%)
Year published:	
1990–1994	6 (14.3%)
1995–1999	6 (14.3%)
2000–2004	15 (35.7%)
2005–2010	13 (31.0%)
2011	2 (4.8%)
Setting:	
Urban	4 (9.5%)
Rural	10 (23.8%)
Both	28 (66.7%)
Case definitions*	
Chinese Classification of Mental Disorders (CCMD)–II:	9 (21.4%)
CCMD–II–R	11 (26.2%)
CCMD–III	8 (19.1%)
DSM–III–R	4 (9.5%)
DSM–IV	4 (9.5%)
ICD–9	2 (4.8%)
ICD–10	10 (23.8%)

DSM – Diagnostic and Statistical Manual of Mental Disorders, ICD – International Classification of Diseases
*Proportions do not add up to 100% because several studies used both CCMD and DSM/ICD case definition.

Study design

The main aim of this study was to estimate the prevalence of schizophrenia in China over two decades of intense development (1990–2010). China is a particularly appropriate setting for studying the effect of development, industrialization and urbanization because of a well–documented administrative categorization of its population into rural and urban areas, thus preventing major misclassification [19–21]. We therefore considered estimates of prevalence (point and lifetime) to be the dependent variable, while the year of study and urban/rural residency were the key predictors. We relied on point prevalence as the primary outcome for testing the hypothesis on the effect of development on the prevalence of schizophrenia. This is because point prevalence was based on direct assessment of study subjects, while lifetime prevalence was prone to self–assessment bias and recall bias. Therefore, we considered point prevalence a more reliable indicator of disease frequency for the purpose of hypothesis testing. However, we used lifetime prevalence in assessing the population–attributable risk (PAR) associated with development, industrialization

Figure 2. Geographic location of 48 study sites in 42 retained studies. The studies are shown on the map of China that represents the areas of urban and rural areas (I– most developed; IV–least developed) around the mid–point of the study period.

and urbanization, because it was consistently larger than point prevalence and it therefore provided more useful policy–relevant information. Relying on point prevalence for this purpose would lead to an underestimate of the size of the problem in China.

Statistical analyses

Based on the retained 42 studies, Bayesian methods (see eMethods in **Online Supplementary Document**) were applied to predict maximum likelihood for point prevalence and lifetime prevalence in urban and rural areas of China in the years 1990, 2000 and 2010, together with 95% credible intervals. The computed probabilities were then applied to the population of China aged 15 years and above in the corresponding years in both the rural and urban settings to derive the expected number of cases ("burden"). In this model, "point prevalence" refers to the probability that a randomly sampled individual from an urban or rural setting has schizophrenia in a given year (1990, 2000 or 2010), while "lifetime prevalence" refers to the probability that the same individual reported having been diagnosed with schizophrenia during his/her lifetime by the given year. The population size of China for 1990, 2000 and 2010 was obtained from the United Nations Population Division [11] while the proportion of urban residency for the corresponding years was obtained from census conducted by the National Bureau of Statistics of China [18].

To explore the effect of two other possible covariates – the distribution of subjects within each sample by sex and age – on which we did not have complete information from all studies, we conducted a separate sensitivity analysis using all the studies in our data set that provided information on age and gender of the examinees. We evaluated the effects of mean age of the sample and male–to–female ratio on the point and lifetime prevalence of schizophrenia using Bayesian methods described in eMethods in **Online Supplementary Document**.

RESULTS

Bayesian analyses of the 42 studies combined information from 2 284 957 people tested for schizophrenia, 10 506 of whom were diagnosed with the disease at some point in their lives. Analyses of the point prevalence data suggested that the increase in prevalence was significant in urban areas, but not in rural areas (eMethods in **Online Supplementary Document**). This finding was corroborated with a separate analysis of the data on lifetime prevalence, which showed a significant and positive effect of the year of study in both the rural and the urban settings, confirming a significant increase in the prevalence of schizophrenia over the two decades.

Based on those results, it is possible to estimate the probabilities of having schizophrenia in 1990, 2000 and 2010 in urban and rural settings, together with a 95% credible interval. **Table 2** shows that, in urban areas of China, the point prevalence in the population aged 15 years or older was 0.32% (0.29–0.36%) in 1990, 0.47% (0.44–0.50%) in 2000 and 0.68% (0.57–0.81%) in 2010. In contrast, in rural areas, the corresponding probabilities were 0.37% (0.33–0.42%), 0.36% (0.35–0.38%), and 0.35% (0.33–0.38%). Lifetime prevalence in the population aged 15 years or older in urban China was 0.39% (0.37–0.41%) in 1990, 0.57% (0.55–0.59%) in 2000 and 0.83% (0.75–0.91%) in 2010. The corresponding probabilities for rural areas were 0.37% (0.34–0.40%), 0.43% (0.42–0.44%), and 0.50% (0.47–0.53%) (**Table 2**).

Applying those probabilities to the corresponding population estimates for China and taking into account the percentage living in urban areas in 1990, 2000 and 2010, it is estimated that there were 3.09 (2.87–3.32) million persons in China affected with schizophrenia during their lifetime in the year 1990. 27% of the cases were from urban areas, which is comparable to the population of China categorized as "urban" in 1990 in demographic records [11]. By 2010, the number of persons ever affected with schizophrenia has risen sharply to 7.16 (6.57–7.75) million – a 132% increase – while the total population of China only in-

Table 2. Estimates of lifetime and point prevalence of schizophrenia in urban and rural settings in China for the year 1990, 2000 and 2010 (with 95% credible intervals)*

Outcome/Setting	Year		
	1990	**2000**	**2010**
Point prevalence:			
Urban	0.32% (0.29–0.36%)	0.47% (0.44–0.50%)	0.68% (0.57–0.81%)
Rural	0.37%(0.33–0.42%)	0.36% (0.35–0.38%)	0.35% (0.33–0.38%)
Lifetime prevalence:			
Urban	0.39% (0.37–0.41%)	0.57% (0.55–0.59%)	0.83% (0.75–0.91%)
Rural	0.37% (0.34–0.40%)	0.43% (0.42–0.44%)	0.50% (0.47–0.53%)
Number of cases of disease (in thousands):			
Urban	849 (805–892)	1935 (1867–2003)	4412 (3987–4837)
Rural	2245 (2063–2427)	2607 (2546–2667)	2744 (2580–2901)
All China	3094 (2868–3319)	4542 (4413–4670)	7156 (6566–7748)

*The estimates are based on Bayesian methods and represent the median of posterior distribution of probability of having schizophrenia in the year 1990, 2000 and 2010. Computation of the number of cases is based on estimates of lifetime prevalence.

creased by 18% during this period [11]. Moreover, the contribution of expected cases from developed urban areas to the overall burden increased from 27% in 1990 to 62% in 2010, well above the proportion of urban residents in China in 2010 that was just below 50% (**Figure 3**) [11].

DISCUSSION

Our study suggests that in 1990, the probability that people would suffer from schizophrenia was very similar in rural and urban China. In urban areas, however, the prevalence rose steeply over the 20–year period, approximately doubling by 2010. We can be reasonably confident in our assessment of the prevalence and trend of schizophrenia cases in China over this period of rapid urbanization (1990–2010). This is in part because of the relatively large number of high quality studies that we were able to obtain from the Chinese databases. These studies gave us an unprecedentedly large overall sample size upon which our estimates were based. All studies included in our analyses were based on a consistent rural/urban separation that used the comparable case definition over the 20–year period [19–21]. Chance effects in our estimates were minimized because the studies were very large, spread over 21 of China's 31 provinces, municipalities and autonomous regions (as shown in Table s4 in **Online Supplementary Document**), applied comparable internationally recognized 'gold standard' case def-

initions of schizophrenia and used stringent data collection methods. Bayesian methods of analyses were suited to the study as they make good use of data sets based on very large sample size [22].

It is useful to compare our estimates with historic estimates that emerged from national surveys of psychiatric disorders that were performed in collaboration with the World Health Organization in 1982 and 1993 [23,24]. Based on those large multi–province efforts, Phillips et al. estimated that 4.25 million people in China were living with schizophrenia in the period 1995–1999 [24]; in another study they estimated 4.77 million cases in 1999 [23]. In our study, we estimated 4.54 (4.41–4.67) million cases in 2000, which is very similar to both of those previous estimates and falls between them. Moreover, Phillips et al. estimated that the prevalence of schizophrenia was higher in urban than rural areas (RR = 1.62 [1.10–2.40]), with exact values for 1993 of 6.71 per 1000 (59/8799) for the urban point prevalence, and 4.13 per 1000 (43/10424) for a rural point prevalence [24]. We conducted a similar analysis on a much larger sample derived from ten studies that explored the prevalence in both rural and urban population from the same geographic setting, using the same study design and methods of case ascertainment (see Table s5 in **Online Supplementary Document**). We obtained estimates of 6.4 per 1000 (480/74 925) for urban and 4.4 per 1000 (342/77 529) for rural point prevalence. Again, those estimates are very similar and supportive of each other, providing additional validity to our findings [24,25].

In addition, biases in estimates are limited by the exclusion of studies with special populations, and by performing an additional sensitivity analysis for the effects of age and gender distribution within the samples on the reported prevalence. Through the latter, we were able to exclude the role of mean age as a significant predictor and to establish higher rates among males. Given that male–to–female ratio across all studies was comparable to the population of China, no further adjustments were required (eMethods in **Online Supplementary Document**). The effect of development, industrialization and urbanization is unlikely to be partly explained by migrant workers from rural areas increasingly seeking care in urban areas. This is because rural prevalence has not decreased significantly over the same period and because previous studies provide further evidence that such scenario is unlikely [26,27]. Moreover, the possible explanation of affected persons selectively moving from rural to urban areas for treatment is not supported by what is known about care seeking by migrant groups [22,26].

Several further variables could have hypothetically contributed to the results. The first one is a possible difference in level of awareness about the symptoms between rural and
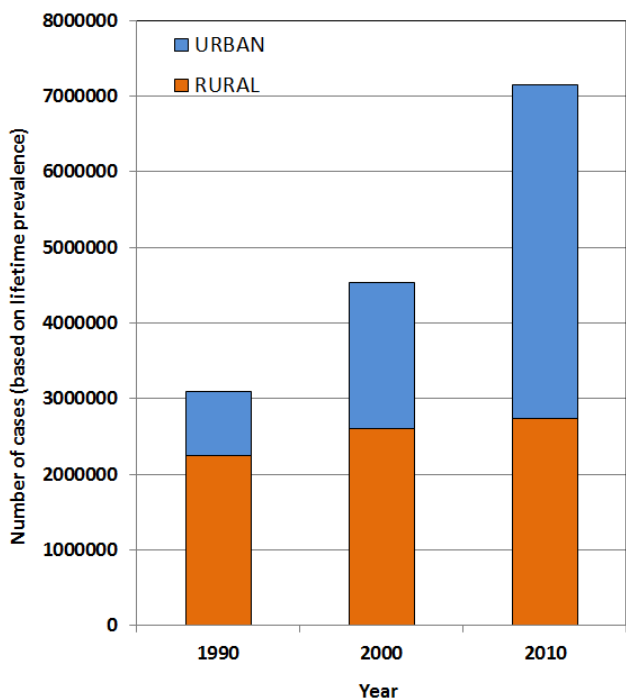
Figure 3. Absolute number of schizophrenia cases in China 1990–2010 by type of residency, based on estimates of lifetime prevalence

urban areas. The second one is related to greater social and occupational demands of urban living vs rural living, that make the limitations and social dysfunction of individuals with schizophrenia more obvious in urban areas. Moreover, social networks may be better developed in rural areas, or attitudes towards psychiatric conditions more negative, resulting in a larger proportion of individuals with schizophrenia being missed, unreported, or refusing to participate in studies. Given that nearly two–thirds of the studies were conducted by the teams of investigators that visited both urban and rural areas, with case definitions applied strictly, we conclude that those potential biases should not be expected to have a major influence on the reported results.

Another hypothetical bias is a possibility of considerably higher fatality of persons with schizophrenia in rural areas, which would remove them from the pool of cases identified in prevalence studies. We found three studies that provided useful information to address this problem [24,28,29]. They all agreed that suicides are still relatively rare among the cases in both areas. Therefore, mortality and fatality rates reported in those studies are not sufficiently large to explain an appreciable portion of the observed differences in prevalence rates.

This study also helps address bias towards high–income countries in studies on the effects of development, industrialization and urbanization in the current literature on schizophrenia. It helps establish the universality of this risk factor and the extent to which it affects the burden of schizophrenia in a large country that underwent rapid urbanization. Such associations could not be have been explored in high–income countries because industrialization had occurred over a much longer period of time, with little reliable epidemiological records.

Nonetheless, there is a number of limitations. The large effect of development, industrialization and urbanization on the prevalence of schizophrenia in China does not imply causality. To this end, our study is able to shed some light on possible mechanisms through which development and urbanization increase the risk of schizophrenia, by lending support to some hypotheses over others. As schizophrenia prevalence was found to be similar in the beginning of this period of industrialization (late 1980s) in both rural and urban China [30,31], our findings suggest that the mechanisms driving the risks of illness in urban areas are likely to be associated with modern urban lifestyles and the development of urban areas. If urban birth or maternal exposure to infectious diseases (linked to higher population density in urban areas) were primarily responsible, then we would have expected notable differences between urban and rural areas across the entire study period, but this was not the case.

We are unable to further explore possible mechanisms due to the lack of information relating to the characteristics of individuals with and without schizophrenia in the original studies, such as their living conditions, degree of isolation, migration status, age of migration, time spent in urban areas, and population density of the individual's place of original and the study sites. Due to the insufficient number of incidence studies identified in our review, we are unable to define the trend of incidence of schizophrenia in China over this period, which could have further informed the ways in which development, industrialization and urbanization affect the rates of schizophrenia. To fully understand these associations, further studies should focus on establishing large high quality and nationally representative cohort with information on different socio–demographic structure and individual characteristics [32,33]. The lower rates of schizophrenia found in the beginning of the study period (in 1990), when China was less industrialized, are consistent with previous studies that reported lower rates of schizophrenia in LMIC [3,4,10]. Previous studies also showed that those affected with schizophrenia in pre–industrialized regions seemed to have a better prognosis for recovery, regardless of a lack of treatment [34,35].

The "population attributable fraction" due to development, industrialization and urbanization cannot be computed in a standard way because this would require the relative risk to be constant over time. In our study, it appears that the relative risk of schizophrenia for urban area residency has been increasing over the past two decades, from being approximately 1.0 to 2.0 or higher. The relative risk of >2.0 is comparable to that reported in studies of urban areas in high–income countries [6,9]. This changing risk of urban area residency in China over the 20–year period makes it difficult to assign a particular proportion of schizophrenia cases to urban area residency in the year 2010. If we accept that the relative risk of urban area residency increased to 2.0 in 2010, then approximately 1.38 million out of 7.16 million cases would be attributable to a change of residency status for the 300 million Chinese whose rural area residency in 1990 changed to urban area residency by 2010. Another way of looking at this problem is to also include the urban residents in 1990 who were exposed to a much higher risk of urban living by 2010, suggesting that up to 3 million schizophrenia cases in 2010 are the "excess" attributable to living in modern, industrialized and developed urban areas (**Figure 3**). These computations are based on two components: (i) increased exposure to "urban area living" in 2010 (in comparison to 1990, one quarter of the population of China moved from "unexposed" rural to "exposed" urban environment); and (ii) increased prevalence in urban environments (with a rough estimate of RR of 2.0 in 2010). This implies that 19.3% of schizophrenia cases in China today may be due to transition from

rural to urban environment, with a further 21.6% might be due to changes in lifestyle among people who were already living in urban environment in 1990.

This work has broad implications. Living in urban areas seems to be the most consistently identified environmental risk factor for schizophrenia in the English literature, with a substantial relative risk and population attributable fraction noted in western countries [6,9]. The relevant Chinese literature reviewed in this study provides additional evidence in support to this observation in a different ethnic population. Many populous parts of the world, particularly in LMIC, are undergoing development, industrialization and urbanization at a scale and rate that took western countries centuries to achieve [36]. Global development, indus-

trialization and urbanization may therefore result in an increased global prevalence of schizophrenia through mechanisms that need to be further explored. Recently, a landmark study that investigated the genetic basis of schizophrenia was published, showing that "…*associations (between genetic variants and schizophrenia) were enriched among genes expressed in tissues that have important roles in immunity, providing support for the speculated link between the immune system and schizophrenia*" [37]. Given that improved sanitation and decreased exposure to infections are one of the main consequences of urbanization, this unexpected finding further underscores the importance of further epidemiological exploration of an apparent association between urbanization and schizophrenia.

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PAPERS

Geographic epidemiology of cardiometabolic risk factors in middle class urban residents in India: cross–sectional study

Rajeev Gupta[1], Krishna Kumar Sharma[1], Bal Kishan Gupta[2], Arvind Gupta[3], Banshi Saboo[4], Anuj Maheshwari[5], Tulika Mahanta[6], Prakash C Deedwania[7]

[1] Fortis Escorts Hospital, Jaipur, India
[2] SP Medical College and Associated Group of Hospitals, Bikaner, India
[3] Jaipur Diabetes Research Centre, Jaipur, India
[4] Diabetes Care and Hormone Clinic, Ahmedabad, India
[5] BBD College of Dental Sciences, Lucknow, India
[6] Assam Medical College, Dibrugarh, India
[7] University of California San Francisco, Fresno, California, USA

Correspondence to:

Dr Rajeev Gupta
Department of Medicine
Fortis Escorts Hospital
JLNMarg
Jaipur 302017 India
rajeevgg@gmail.com

Objective To determine epidemiology of cardiovascular risk factors according to geographic distribution and macrolevel social development index among urban middle class subjects in India.

Methods We performed cross-sectional surveys in 11 cities in India during years 2005–2009. 6198 subjects aged 20–75 years (men 3426, women 2772, response 62%) were evaluated for cardiovascular risk factors. Cities were grouped according to geographic distribution into northern (3 cities, n = 1321), western (2 cities, n = 1814), southern (3 cities, n = 1237) and eastern (3 cities, n = 1826). They were also grouped according to human social development index into low (3 cities, n = 1794), middle (5 cities, n = 2634) and high (3 cities, n = 1825). Standard definitions were used to determine risk factors. Differences in risk factors were evaluated using χ^2 test. Trends were examined by least squares regression.

Findings Age–adjusted prevalence (95% confidence intervals) of various risk factors was: low physical activity 42.1% (40.9–43.3), high dietary fat 49.9% (47.8–52.0), low fruit/vegetables 26.9% (25.8–28.0), smoking 10.1% (9.1–11.1), smokeless tobacco use 9.8% (9.1–10.5), overweight 42.9% (41.7–44.1), obesity 11.6% (10.8–12.4), high waist circumference 45.5% (44.3–46.7), high waist–hip ratio 75.7% (74.7–76.8), hypertension 31.6% (30.4–32.8), hypercholesterolemia 25.0% (23.9–26.9), low HDL cholesterol 42.5% (41.3–43.7), hypertriglyceridemia 36.9% (35.7–38.1), diabetes 15.7% (14.8–16.6), and metabolic syndrome 35.7% (34.5–36.9). Compared with national average, prevalence of most risk factors was not significantly different in various geographic regions, however, cities in eastern region had significantly lower prevalence of overweight, hypertension, hypercholesterolemia, diabetes and metabolic syndrome compared with other regions ($P < 0.05$ for various comparisons). It was also observed that cities with low human social development index had lowest prevalence of these risk factors in both sexes ($P < 0.05$).

Conclusions Urban middle–class men and women in eastern region of India have significantly lower cardiometabolic risk factors compared to northern, western and southern regions. Low human social development index cities have lower risk factor prevalence.

Cardiovascular diseases are one of the most important causes of morbidity and mortality in low and middle income countries, including India [1]. However, there are substantial within–country variations in cardiovascular morbidity and studies in Europe and North America have reported substantial national, urban–rural and regional variations in cardiovascular disease incidence and mortality [2,3]. These differences are due to variations in lifestyles (dietary factors, physical activity and smoking), biological risk factors (hypertension, lipid levels, diabetes and metabolic syndrome) and social factors [1]. Macrolevel social factors [4] could be important causes of these differences but have not been well studied. Macro–level factors that influence cardiovascular risk are area based measures (urban or rural), measures of living conditions, measures of income inequality, human development index and status of health care delivery [4,5]. Individual–level social factors are social status, education, income, occupation, employment status, lifespan social class, and factors that influence adherence to lifestyles and medical treatment [5].

In India, significant geographic variations in cardiovascular mortality have been reported [6]. Studies have also reported significant urban–rural differences in cardiovascular morbidity and risk factors [7]. Studies which used similar methodology reported greater prevalence of obesity, abdominal obesity, hypertension, hypercholesterolemia and diabetes in urban as compared to rural populations [8-11]. Reviews have reported significant geographic differences in prevalence of smoking [12], obesity [13], hypertension [14], dyslipidemia [15], and diabetes [16] in India. These geographic differences in cardiovascular risk factors could be due to ethnic and sociocultural differences as well as differences in macrolevel socioeconomic factors such as degree of urbanization and human and social development indices [17]. Study of macrolevel factors is important because these are influenced by national and regional policies and quality of local governance [4,5]. Moreover, macrolevel factors are better amenable to social engineering [18]. Social engineering has been defined as a process through which the state can improve education, health care, housing and other basic facilities to improve quality of life and address problems of ill–health, poverty, unemployment and slow development [19].

Urbanization is rapidly increasing in India and this population is poised to increase from the current 400 million (35% of the country) to more than a billion in the next 30 years [20]. There is, therefore, a need to evaluate current prevalence of cardiometabolic risk factors in India, especially urban locations. There is also a need to evaluate risk factors in the urban middle–class which is one of the larger segments of Indian society [21]. It has been predicted that in the next 30 years more than 70% of the national

population shall be urban and most would be in the middle class [20,21]. Accordingly, we designed the India Heart Watch study to identify prevalence of cardiometabolic risk factors among middle–class subjects living in urban locations in different regions of India [22]. We defined middle–class subjects as those living in middle–class locations as defined by local municipal councils. Although there could be state–level variations in such definitions, previous reports from India have shown insignificant heterogeneity [23]. To determine macrolevel determinants of cardiovascular risk factors in the urban middle–class, we first evaluated influence of geographic differences after dividing the country into four regions– north, south, east and west with 2–3 cities in each (**Figure 1**). There is a significant socioeconomic heterogeneity in various geographic regions of the country [23,24]. Eastern and central Indian regions as well as some states in northern India (called empowered action groups states) are less developed as compared to western and southern regions [24]. This may vitiate the geographic differences which also include regional and local socioeconomic development [23-25]. Therefore, to better determine macrolevel determinants of cardiovascular risk, we used a novel social development index which is a measure of poverty and its social determinants and is a composite of demography, health care, basic amenities, education, economic deprivation and social deprivation (**Table 1**) [25].

METHODS

A multisite study to identify prevalence of cardiovascular risk factors and their socio–demographic determinants was

Figure 1. Map of India showing various locations in the India Heart Watch study.

Table 1. Indicators, database indicators and database used in estimation of social development index

Demographic indicators	Contraceptive prevalence rate Total fertility rate Infant mortality rate
Health indicators	Percentage of institutional deliver Percentage of undernourished children
Educational attainment indicators	Literacy rate Pupil–teacher ratio School attendance rate
Basic amenities indicators	Percent households which live in *pucca* house Households with access to safe drinking water Households with access to toilet facility Households with electricity connection
Economic deprivation indicators	Household economic date from National Sample Survey 61st round (2004–5) and 62nd round (2005–6)
Social deprivation indicators	Disparity ratio between scheduled castes and general population in literacy rates Disparity ratio between scheduled tribes and general population in literacy rates Male–female disparity ratio in education Female–total unemployment rate ratio Disparity ratio of per capita expenditure of Muslim population with total population Child sex ratio

organised among urban subjects in India. Rationale for the study has been reported earlier [22]. Protocol was approved by the institutional ethics committee of the national coordinating centre. Written informed consent was obtained from each participant. The study performa was developed according to recommendations of the World Health Organization (WHO) [26].

Regions and investigators

We planned the study to identify prevalence of cardiometabolic risk factors and their determinants among urban subjects in India [27]. Medium sized cities were identified in each of the large states of India and investigators who had a track record of research in cardiovascular or diabetes epidemiology were invited to participate. 20 investigators were invited from all large states of India and 11 participated. A steering committee meeting with all the investiga-

tors was organised at initiation of the study where the study protocol was discussed and developed. The meeting was followed by training in salient features of questionnaire and techniques of evaluation to ensure uniformity in recruitment and data collection. The cities are in northern (Jammu, Chandigarh, Bikaner), western (Ahmadabad, Jaipur), eastern (Lucknow, Patna, Dibrugarh) and southern (Madurai, Belgaum, Nagpur) regions of India (**Figure 1**). Salient demographic characteristics of these cities are shown in **Table 2**.

Sampling

The study data were collected in the years 2006–2010. Simple cluster sampling was performed at each site. A middle–class location was identified at each city based on municipal classification derived from cost of land, type of housing, public facilities (roads, sanitation, water supply,

Table 2. Socio–demographic characteristics of the study sites

Location (City, State)	Population in millions (Census 2011)	Females/1000 Males	Literacy rate (%)	Urban slums (%)	Human Development Index	Social Development Index	Present study sample
Northern India							
Jammu (Jammu & Kashmir)	0.51	889	89.6	–	0.529	0.51	320
Chandigarh (Chandigarh)	0.96	818	86.0	13.2	0.784	0.77	502
Bikaner (Rajasthan)	0.65	852	66.0	18.5	0.434	0.38	499
Western India							
Ahmedabad (Gujarat)	6.36	897	89.0	13.5	0.577	0.67	490
Jaipur (Rajasthan)	3.05	907	76.4	15.1	0.434	0.51	1324
Southern India							
Belgaum (Karnataka)	0.61	969	78.0	11.0	0.519	0.66	50
Nagpur (Maharashtra)	2.50	961	93.1	35.9	0.572	0.73	264
Madurai (Tamilnadu)	1.47	999	81.9	23.8	0.570	0.73	923
Eastern India							
Lucknow (Uttar Pradesh)	2.90	923	84.7	8.2	0.380	0.34	835
Patna (Bihar)	1.68	882	84.7	0.3	0.367	0.23	491
Dibrugarh (Assam)	0.15	952	89.5	–	0.444	0.63	500

electricity, gas supply, etc.), and educational and medical facilities as reported earlier [27]. Sample size of about 250 men and 250 women (n = 500) at each site is considered adequate by the WHO to identify 20% difference in mean level of biophysical and biochemical risk factors [26]. The sample size required for 85% chance of recognizing a specified difference in rates (power 1–β) between two populations, significant at 5% level in a two–tailed test, when true prevalence rates are 10% and 5% is 490 subjects. These prevalence rates are similar to previous studies on diabetes prevalence (the lowest prevalent cardiovascular risk factor) from India. For continuous variables this sample size would have 85% chance of recognizing a difference in mean value of 1 with SD of 5 [26]. Accordingly, we invited 800–1000 subjects in each location to ensure participation of at least 500 subjects at each site estimating a response of 70% as reported in previous studies [28]. Sample sizes at some sites was low due to low recruitments (eg, Belgaum) and oversampling was performed at high recruiting sites (eg, Jaipur, Madurai) to have adequate geographic representation (**Table 2**). At each site a uniform protocol of recruitment was followed [27]. The surveys were preceded by meetings with community leaders to ensure good participation. Subjects were invited in fasting state to a community centre of medical centre within each locality either twice or thrice a week depending upon the investigator's schedule. Inclusion criteria were all adults aged ≥20–75 years living in the particular location. Subjects who were confined to home with severe debilitating disease, those not likely to survive beyond 6 months and pregnant women were excluded.

Measurements

The study performa was filled by the research worker employed by the site investigator after details were inquired from the subject. Apart from demographic history, details of educational status, history of known hypertension, diabetes, lipid abnormalities and cardiovascular disease were inquired [27]. Details regarding smoking and smokeless tobacco use, alcohol intake, dietary fat and fruits and vegetables intake were assessed as reported previously [29]. Details of physical activity were inquired for exact daily duration (minutes) of work related, commute related and leisure time physical activity [29]. Equipments for measurement of height, weight, waist and hip size and blood pressure were similar to ensure uniformity as suggested by WHO guidelines [26]. Sitting blood pressure was measured after at least 5-minute rest using standardised instruments. Three readings were obtained and were averaged for the data analysis. Fasting blood sample was obtained from all individuals after 8–10 hours fast. Fasting state was determined according to self–reports. The blood samples were obtained at community centres by technicians from

an accredited national laboratory– Thyrocare Technologies Ltd, Mumbai, India (www.thyrocare.com). Blood glucose was measured at the local biochemistry facility of these laboratories. Blood for cholesterol, cholesterol lipoproteins and triglycerides estimation was transported under dry ice to the national referral laboratory where all the blood samples were analysed using uniform protocol. Cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride levels were measured using enzyme–based assays with internal and external quality control (www.thyrocare.com) as reported earlier [30]. Values of low density lipoprotein (LDL) cholesterol were calculated using Friedwald's formula: LDL cholesterol = total cholesterol – (HDL cholesterol + triglycerides/2.17).

Diagnostic criteria

The cities were grouped into four geographic regions– northern, western, southern and eastern (**Figure 1**). Demographic details of the cities are shown in **Table 2**. Although the population of the cities varied from more than 6 million (Ahmedabad) to less than half a million, they are not very dissimilar in other socio–demographic characteristics such as literacy, housing and human development index (**Table 2**). Cities were also grouped according to urban social development index. Computation of social development index is similar to human development index developed by the United Nations Development Program and uses the range equalization method wherein each indicator is divided by range of the particular indicator so that scale–free values vary between zero and unity (**Table 1**) [25]. Details of its calculation for Indian urban locations are provided in the publication [25]. This index is a measure of poverty and its social and health manifestations (demographic and health indicators) and their social determinants (education, economic deprivation, social deprivation and amenities). The cities were classified according to this index into tertiles of high (Chandigarh 0.77, Madurai 0.73, and Nagpur 0.73), medium (Ahmedabad 0.67, Belgaum 0.66, Dibrugarh 0.63, Jaipur 0.51, Jammu 0.51) and low (Bikaner 0.38, Lucknow 0.34, Patna 0.23) human social development index.

Details of other diagnostic criteria have been reported earlier [27]. Smokers included subjects who smoked cigarettes, *bidis*, or other smoked forms of tobacco daily, past smokers were subjects who had smoked for at least 1 year and had stopped more than a year ago. Users of other forms of tobacco (oral, nasal, etc) were classified as smokeless tobacco use. Subjects consuming ≥20 g visible fat daily were categorized as high fat intake. This corresponds to total fat intake of >40 g/d reported in a previous study from India [31] and corresponds to percent energy intake from fat (fat en%) of >30% [32]. The WHO has defined low fruits and

vegetables intake as <5 servings per day [32]. However, using this cut off, almost all the study subjects were under the low intake criteria, therefore, we used the sample median, and classified ≤2 servings of fruits or vegetables daily, as low intake. Those involved in any significant physical activity were classified as active and with >30 minutes of work–, leisure–, or commute–related physical activity were classified as moderately active. Hypertension was diagnosed when systolic blood pressure was ≥140 mm Hg and/or diastolic ≥90 mm Hg or a person was a known hypertensive. Overweight was defined as body mass index ≥25 kg/m^2 and obesity defined by body mass index ≥30 kg/m^2. Truncal obesity was diagnosed when waist–hip ratio was >0.9 in men and >0.8 in women or waist circumference was >90 cm in men and >80 cm in women according to the international harmonised guidelines [33]. Dyslipidemia was defined by the presence of high total cholesterol (≥5.2 mmol/L), high LDL cholesterol (≥3.4 mmol/L), low HDL cholesterol (<1.0 mmol/L in men and <1.3 mmol/L in women) or high triglycerides (≥1.7 mmol/L), or if the individual was on treatment with cholesterol–lowering drugs according to US National Cholesterol Education Program [34]. Diabetes was diagnosed on the basis of either history of known diabetes on treatment or fasting glucose ≥7 mmol/L, similar definition was used in our previous report [35]. The diagnosis of the metabolic syndrome was based on the harmonized Asian criteria [33], and was diagnosed when any three were present out of the following five: waist size >90 cm men, >80 cm women; BP systolic ≥130 and/or diastolic ≥85 mm Hg; fasting triglycerides ≥1.7 mmol/L; HDL cholesterol <1.0 mmol/L men, <1.3 mmol/L women; and fasting blood glucose >5.5 mmol/L or known diabetes.

Statistical analyses

All the case–data were entered into a SPSS database (Version 10.0, SPSS Inc, Chicago). More than 90% data for various variables were available and in more than 85% subjects the data for all the variables were available. For risk factors, the prevalence rates (%) and 95% confidence intervals (CI) for men and women are reported separately. Age–adjustment was performed using direct method with 2001 Indian census population as standard. Prevalence of risk factors in various geographical and social development index groups is reported as percent with 95% CI. Intergroup comparisons have been performed using χ^2 test. For geographic differences in risk factors we determined differences in prevalence rates in cities in eastern region (where low prevalence of many risk factors was observed) with cities in northern, western and southern regions using χ^2 test. The χ^2 test was also performed to identify significance of difference in prevalence of various risk factors in low vs medium and high social index development cities. Trends in risk factors in low, medium and high social development

index groups have been examined using least–squares regression and R^2 values calculated. P values of <0.05 are considered significant.

RESULTS

The study was performed at 11 cities in India (**Figure 1**). 6198 subjects (men 3426, women 2772) of the targeted 9900 subjects were evaluated (response 62%). Recruitment at individual sites, as proportion of total recruited, was Ahmadabad 490 (7.9%), Bikaner 499 (8.1%), Belgaum 50 (0.8%), Chandigarh 502 (8.1%), Dibrugarh 500 (8.1%), Jaipur 1324 (21.4%), Jammu 320 (5.2%), Lucknow 835 (13.5%), Madurai 923 (14.9%), Nagpur 264 (4.3%) and Patna 491 (7.9%). Data for social and demographic characteristics in men and women have been reported earlier [27]. Men were slightly older than women and there was no significant difference across various age–groups. Low educational status (<10 years of formal education) was more present among women (47.6%) as compared to men (22.3%) and majority of subjects belonged to middle socioeconomic status. More than half of all men and women lived in joint families and 85.6% were married.

Prevalence of various cardiovascular risk factors (age–adjusted prevalence, 95% CI) in the whole group and in men and women are reported in the **Table 3**. There is low prevalence of smoking, smokeless tobacco use as well as alcohol intake in men and women while prevalence of low fruit and vegetable intake, high visible fat intake and sedentary lifestyle is moderate to high. Prevalence of biophysical and biochemical risk factors is also moderate to high.

We grouped the cities into northern (Jammu, Chandigarh, Bikaner), western (Ahmadabad, Jaipur), eastern (Lucknow, Patna, Dibrugarh) and southern (Madurai, Belgaum, Nagpur) (**Table 2**). Age–adjusted prevalence of various cardiovascular risk factors in men and women at different geographical locations are shown in **Table 4**. We compared prevalence of lifestyle and cardiometabolic risk factors in eastern region cities with others. This shows that among eastern regional urban participants there is lower prevalence of overweight, hypertension, hypercholesterolemia, diabetes and metabolic syndrome. Participants from northern and southern regions have the highest prevalence of hypertension, hypercholesterolemia and low HDL cholesterol. Prevalence of diabetes and metabolic syndrome is highest among participants in the northern and southern regions. Compared with the national average (from **Table 3**), there is a trend towards greater prevalence of smoking in eastern, truncal obesity in northern, hypertension in northern and eastern, hypercholesterolemia in northern, diabetes in northern and southern and metabolic syndrome in northern and southern Indian cities. However, these differences are not statistically significant.

Table 3. Age–adjusted prevalence of lifestyle and cardiometabolic and lifestyle risk factors in men and women*

Variables	Total N = 6198	Men N = 3426	Women N = 2772
Sedentary lifestyle (<moderate physical activity)	42.1 (40.9–43.3)	38.8 (37.2–40.4)	46.1 (44.2–48.0)
Visible fat intake:			
20–40 g/d	35.8 (34.6–37.0)	36.6 (35.0–38.2)	34.7 (32.9–36.5)
>40 g/d	14.1 (13.2–15.0)	14.6 (13.4–15.8)	13.5 (27.2–30.6)
Fruits and vegetables intake (≤2 servings/d)	26.9 (25.8–28.0)	25.3 (23.8–26.8)	28.9 (27.2–30.6)
Smoking:			
Current smokers	6.9 (6.3–7.5)	12.0 (10.9–13.1)	0.5 (0.2–0.7)
Ex–smokers	3.2 (2.8–3.6)	5.1 (4.4–5.8)	0.9 (0.5–1.3)
Smokeless tobacco use	9.8 (9.1–10.5)	12.7 (11.6–13.8)	6.3 (5.3–7.2)
Alcohol consumption:			
<7 drinks/week	7.6 (6.9–8.3)	12.5 (11.4–13.6)	1.5 (1.1–2.0)
≥7 drinks/week	0.3 (0.2–0.4)	0.6 (0.3–0.6)	–
Obesity:			
BMI ≥25 kg/m²	42.9 (41.7–44.1)	41.1 (39.4–42.7)	45.2 (43.3–47.1)
BMI ≥30 kg/m²	11.6 (10.8–12.4)	8.3 (7.4–9.2)	15.8 (14.4–17.2)
Truncal obesity:			
Waist >90/>80 cm, men/women	45.5 (44.3–46.7)	35.7 (34.1–37.3)	57.5 (55.7–59.0)
WHR >0.9/>0.8, men/women	75.7 (74.7–76.8)	69.0 (67.5–70.6)	83.8 (82.9–85.2)
Hypertension	31.6 (30.4–32.8)	32.5, 30.9–34.1)	30.4 (28.7–32.1)
High total cholesterol (≥5.2 mmol/L)	25.0 (23.9–26.9)	24.8, 23.3–26.3)	25.3 (23.7–26.9)
High triglycerides (≥1.7 mmol/L)	36.9 (35.7–38.1)	41.2, 39.5–42.9)	31.5 (29.8–33.2)
Low HDL cholesterol (men <1.0/ mmol/L woman <1.3 mmol/L)	42.5 (41.3–43.7)	34.1, 32.5–35.7)	53.0 (51.1–54.9)
Diabetes (known or fasting glucose ≥7.0 mmol/L)	15.7 (14.8–16.6)	16.7, 15.5–17.9)	14.7 (13.4–16.0)
Metabolic syndrome	35.7 (34.5–36.9)	32.2 (30.6–33.8)	40.4 (38.6–42.2)

BMI – body mass index, WHR – waist hip ratio, HDL – high density lipoprotein
*Prevalence in percent and 95% confidence intervals in parentheses.

The cities were also classified according to human social development index into tertiles of low, mid and high groups. Prevalence of various lifestyle and cardiometabolic risk factors in different social development index groups and significance of differences in their prevalence in low vs medium and high social development cities is shown in **Table 5**. Prevalence of smokeless tobacco use, high visible fat intake and low fruits and vegetables intake is greater in participants from low social development index cities as compared to medium and high development cities while low physical activity is more among women in high index cities. Prevalence of cardiometabolic risk factors (overweight/obesity, high waist circumference in men, hypertension, high total cholesterol, diabetes and metabolic syndrome) is significantly greater among participants from cities with medium and high social development index. Prevalence of low HDL cholesterol is more in low social development index cities.

Age and sex–adjusted prevalence of various cardiometabolic risk factors in subjects in dif-ferent geographic locations and social development index cities are shown in **Figures 2** and **3**, respectively. For geographic locations, there are no significant linear trends in
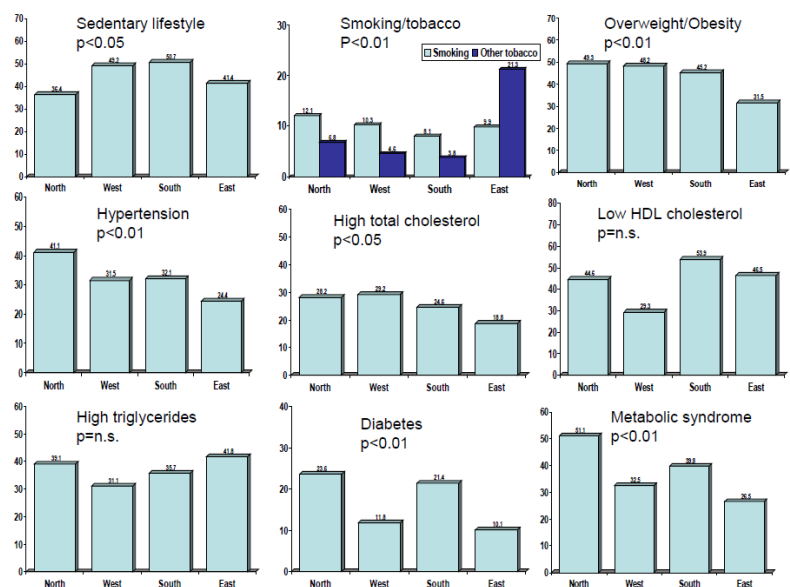
Figure 2. Prevalence of various cardiometabolic risk factors in different geographic regions of India (age– and sex–adjusted). Overweight/obesity, hypertension, high total cholesterol, diabetes and metabolic syndrome is lowest in the cities of eastern region while tobacco use is the highest (p values in Table 4).

Table 4. Age–adjusted prevalence of various cardiovascular risk factors at cities in eastern, northern, western and southern regions*

|	Men				Women			
	Eastern	Northern	Western	Southern	Eastern	Northern	Western	Southern
	N = 1101	N = 713	N = 1062	N = 550	N = 725	N = 608	N = 752	N = 687
Physical activity (≥moderate)	47.0 (44.0–49.9)	22.3 (19.2–25.3)	43.0 (40.0–45.9)	42.9 (38.7–47.0)	32.8 (29.4–36.2)	31.2 (27.5–34.0)	57.8 (54.3–61.3)	57.0 (53.3–60.7)
Eastern vs others†	–	11.3, <0.001	3.5, 0.060	2.5, 0.111	–	0.38, 0.538	93.1, <0.001	83.8, <0.001
Visible fat intake ≥20 g/d	53.0 (50.0–55.9)	53.4 (49.7–57.1)	52.2 (49.2–55.2)	43.1 (38.9–47.4)	54.5 (50.1–58.1)	47.2 (43.2–51.8)	52.2 (48.5–55.6)	38.4 (34.7–42.0)
Eastern vs others†	–	0.03, 0.869	0.13, 0.715	14.5, <0.001		7.02, 0.008	0.82, 0.364	36.5, <0.001
Fruit/vegetable intake ≤2 servings/d	22.5 (20.0–25.0)	23.4 (20.3–26.5)	30.0 (27.2–32.7)	24.3 (20.7–27.9)	16.8 (14.1–19.5)	24.0 (20.6–27.4)	38.7 (35.2–42.2)	35.4 (31.8–39.0)
Eastern vs others†	–	0.20, 0.657	15.8, <0.001	0.70, 0.408	–	10.6, 0.001	87.6, <0.001	63.3, <0.001
Smoking	16.0 (13.8–18.2)	20.7 (17.7–23.7)	16.1 (13.9–18.3)	16.5 (13.4–19.6)	0.7 (0.09–1.3)	2.0 (0.89–3.1)	2.2 (1.1–3.2)	1.1 (0.32–1.9)
Eastern vs others†	–	6.70, 0.009	0.01, 1.000	0.08, 0.771	–	4.34, 0.037	6.24, 0.013	0.87, 0.350
Smokeless tobacco use	22.0 (19.5–24.4)	11.4 (9.1–13.7)	7.5 (5.9–9.1)	5.4 (3.5–7.3)*	21.3 (18.3–24.3)	1.2 (0.33–2.1)	0.4 (–0.05–0.85)	2.4 (1.2–3.5)
Eastern vs others†	–	32.9, <0.001	89.9, <0.001	73.4, <0.001	–	115.7, <0.001	159.8, <0.001	108.9, <0.001
Overweight (BMI ≥25 kg/m^2)	34.4 (31.3–36.9)	44.7 (41.0–48.3)	47.0 (40–50)	38.7 (34.6–42.8)	27.3 (24.0–30.5)	54.6 (50.6–58.5)	49.9 (46.3–53.5)	50.5 (46.7–54.2)
Eastern vs others†	–	19.8, <0.001	35.9, <0.001	2.83, 0.092	–	102.8, <0.001	79.1, <0.001	80.1, <0.001
High waist circumference (men/women >90/>80 cm)	21.0 (18.6–23.4)	46.5 (42.8–51.2)	47.8 (44.8–50.8)	30.5 (26.6–34.3)	45.5 (41.9–49.1)	69.2 (65.5–72.9)	61.4 (57.9–64.9)	55.0 (51.2–58.7)
Eastern vs others†	–	132.3, <0.001	173.3, <0.001	18.3, <0.001	–	75.7, <0.001	37.6, <0.001	12.7, <0.001
High waist–hip ratio (men/women >0.9/>0.8)	80.2 (77.8–82.5)	63.7 (60.2–67.2)	60.2 (57.2–63.1)	76.9 (73.4–80.4)	94.5 (92.8–96.1)	76.8 (73.4–80.1)	73.5 (70.3–76.6)	90.5 (88.3–92.7)
Eastern vs others†	–	61.7, <0.001	104.2, <0.001	2.54, 0.111	–	88.0, <0.001	119.4, <0.001	7.46, 0.006
Hypertension	22.4 (19.9–24.8)	42.5 (38.8–46.1)	35.5 (32.6–38.4)	34.3 (30.3–38.3)	27.4 (24.1–30.6)	39.6 (35.7–43.5)	25.9 (22.8–29.0)	30.3 (26.8–33.7)
Eastern vs others†	–	81.4, <0.001	44.9, <0.001	26.1, <0.001	–	22.2, <0.001	0.43, 0.509	1.37, 0.241
High cholesterol (≥5.2 mmol/L)	15.2 (13.1–17.3)	30.6 (27.2–34.0)	29.8 (27.0–32.5)	26.5 (22.8–30.2)	24.2 (21.1–27.3)	25.5 (22.0–28.9)	28.3 (25.1–31.5)	23.0 (19.8–26.1)
Eastern vs others†		60.6, <0.001	60.1, <0.001	30.3, <0.001	–	0.26, 0.608	3.12, 0.077	0.32, 0.570
High triglycerides (≥1.7 mmol/L)	45.3 (42.3–48.2)	42.4 (38.8–46.0)	37.0 (34.1–39.9)	39.6 (35.5–43.7)	36.6 (33.1–40.1)	35.1 (31.3–38.9)	22.9 (19.9–25.9)	32.5 (29.0–36.0)
Eastern vs others†		1.50, 0.214	15.8, <0.001	4.81, 0.028	–	0.33, 0.564	32.5, <0.001	2.4, 0.119
Low HDL cholesterol (men/women <1.0/<1.3 mmol/L	39.9 (37.0–42.8)	34.4 (30.9–37.9)	24.2 (21.6–26.8)	41.1 (37.0–45.2)	56.6 (53.0–60.2)	56.5 (52.5–60.4)	36.4 (32.9–39.8)	64.2 (66.6–67.8)
Eastern vs others†		5.82, 0.008	61.5, <0.001	0.66, 0.820	–	0.01, 1.00	60.1, <0.001	8.60, 0.003
Diabetes	10.9 (9.1–12.7)	26.8 (23.5–30.0)	13.3 (11.2–15.3)	22.0 (18.5–25.4)	8.5 (6.4–10.5)	19.9 (16.7–23.1)	9.7 (7.6–11.8)	20.9 (17.8–23.9)
Eastern vs others†		76.9, <0.001	2.91, 0.089	36.2, <0.001	–	35.9, <0.001	0.59, 0.444	43.6, <0.001
Metabolic syndrome (Harmonized Asian definition)	23.4 (20.9–25.9)*	46.7 (43.0–50.3)	50.8 (47.8–53.8)	33.8 (29.8–37.7)	31.3 (27.9–34.7)	56.4 (52.4–60.3)	30.3 (27.0–33.6)	44.5 (40.8–48.2)
Eastern vs others†		106.7, <0.001	30.0, <0.001	20.1, <0.001	–	85.1, <0.001	0.17, 0.679	26.3, <0.001

BMI – body mass index, HDL – high density lipoprotein

*Prevalence in percent and 95% confidence intervals in parentheses.

†χ^2–test statistic and p value.

risk factor prevalence among participants from different geographic regions (**Figure 2**). **Figure 3** shows that there are significant trends (R^2 values) in sedentary lifestyle (0.99), overweight/obesity (0.87), abdominal obesity (0.88), diabetes (0.74) and metabolic syndrome (0.99) in low vs medium and high social development index groups, while the prevalence of smoking (0.99) shows opposite trend (**Figure 3**).

DISCUSSION

The study shows a high prevalence of cardiometabolic risk factors (hypertension, hypercholesterolemia, hypertriglyceridemia, low HDL cholesterol, diabetes and metabolic syndrome and obesity and abdominal obesity) in Asian Indian urban middle class subjects. These prevalence rates are greater than contemporary regional and national population based studies from different parts in the country [36-44] (**Table 6**). This study shows that metabolic cardiovascular risk factors are lower among participants from cities in eastern India. Study participants living in cities with lower human social development index have lower prevalence of these risk factors.

In India there have been limited nationwide or multisite studies that used uniform methodologies to assess multiple cardiovascular risk factors as done in the present study (**Table 6**). The National Family Health Survey, which is the

Table 5. Age–adjusted prevalence (%) and 95% confidence intervals of cardiovascular risk factors in low, mid and high social development index cities

| VARIABLE	MEN			WOMEN		
	Low SDI (n = 1210)	Mid SDI (n = 1382)	High SDI (n = 834)	Low SDI (n = 615)	Mid SDI (n = 1252)	High SDI (n = 905)
Physical activity (≥moderate)	37.6 (34.9–40.3)	39.3 (36.7–41.9)	39.8 (36.5–43.1)	37.9 (34.1–41.7)	44.7 (41.9–47.4)	53.7 (50.4)
Low SDI vs others†	–	0.84, 0.358	1.00, 0.314	–	7.90, 0.005	36.7, <0.001
Visible fat intake ≥20 g/d	62.1 (59.4–64.8)	51.7 (49.1–54.3)	38.6 (35.3–41.9)	62.4 (58.6–66.2)	49.5 (46.7–52.3)	37.3 (34.1–40.4)
Low SDI vs others†	–	28.7, <0.001	109.7, <0.001	–	27.6, <0.001	92.4, <0.001
Fruit intake <2 servings/d	27.2 (24.7–29.7)	25.7 (23.4–28.0)	21.9 (19.1–24.7)	31.2 (27.5–34.8)	26.2 (23.7–28.6)	31.1 (28.1–34.1)
Low SDI vs others†	–	0.68, 0.410	7.22, 0.007	–	5.21, 0.023	0.01, 0.998
Smoking	17.6 (15.4–19.7)	17.4 (15.4–19.4)	15.7 (13.2–18.2)	0.8 (0.1–1.5)	2.1 (1.3–2.9)	1.0 (0.35–1.65)
Low SDI vs others†	–	0.012, 0.999	1.27, 0.262	–	4.42, 0.035	0.13, 0.716
Other tobacco use	14.6 (12.6–16.6)	16.2 (14.2–18.1)	4.0 (2.7–5.3)	5.0 (3.3–6.7)	10.7 (9.0–12.4)	0.8 (0.22–1.38)
Low SDI vs others†	–	1.22, 0.267	59.4, <0.001	–	16.4, <0.001	21.6, <0.001
Overweight (BMI ≥25 kg/m²)	33.9 (31.2–3.66)	47.2 (44.6–49.8)	41.3 (37.9–44.6)	34.3 (30.5–38.0)	44.0 (41.2–46.7)	54.1 (50.8–57.3)
Low SDI vs others†	–	47.6, <0.001	11.9, <0.001	–	16.7, <0.001	57.9, <0.001
High waist circumference (men/women >90/>80 cm)	31.5 (28.9–34.1)	40.7 (38.1–43.3)	33.6 (30.4–36.8)	57.4 (53.5–61.3)	57.0 (54.2–59.7)	58.3 (55.1–61.5)
Low SDI vs others†	–	23.8, <0.001	0.98, 0.321	–	0.02, 0.879	0.13, 0.714
High waist–hip ratio (men/women >0.9/>0.8)	75.2 (72.8–77.6)	60.2 (57.6–62.8)	74.7 (71.7–77.6)	82.1 (79.1–85.1)	80.4 (78.2–82.6)	89.7 (87.7–91.7)
Low SDI vs others†	–	65.3, <0.001	0.07, 0.795	–	0.76, 0.384	18.3, <0.001
Hypertension	27.3 (24.8–29.8)	35.9 (33.4–38.4)	34.4 (31.2–37.6)	28.4 (24.8–31.9)	30.1 (27.5–32.6)	32.0 (28.9–35.0)
Low SDI vs others†	–	21.6, <0.001	11.6, 0.001	–	0.54, 0.461	2.3, 0.124
High cholesterol (≥5.2 mmol/L)	20.0 (17.7–22.2)	26.9 (24.5–29.2)	28.6 (25.5–31.7)	23.4 (20.0–26.7)	26.8 (24.3–29.2)	24.3 (21.5–27.1)
Low SDI vs others†	–	16.5, <0.001	17.5, <0.001	–	2.51, 0.111	0.25, 0.617
High triglycerides (≥1.7 mmol/L)	42.7 (39.9–45.5)	39.2 (36.6–41.8)	42.2 (38.8–45.5)	31.2 (27.5–34.8)	30.8 (28.2–33.6)	32.8 (29.7–35.8)
Low SDI vs others*†	–	3.29, 0.070	0.05, 0.815	–	0.03, 0.864	0.43, 0.512
Low HDL cholesterol (men/women <1.0/<1.3 mmol/L)	41.6 (38.8–44.4)	25.2 (22.9–27.5)	37.9 (34.6–41.2)	57.0 (53.1–60.9)	44.8 (42.0–47.5)	61.5 (58.3–64.7)
Low SDI vs others†	–	79.3, <0.001	2.91, 0.088	–	24.8, <0.001	3.05, 0.081
Diabetes	13.8 (11.8–15.7)	14.1 (12.3–15.9)	25.3 (22.3–28.2)	10.9 (8.4–13.3)	11.0 (9.3–12.7)	21.5 (18.8–24.2)
Low SDI vs others†	–	0.05, 0.821	43.3, <0.001	–	0.01, 1.00	29.1, <0.001
Metabolic syndrome (Harmonized Asian definition)	29.6 (27.0–32.2)	29.6 (27.2–32.0)	40.2 (36.8–43.5)	13.8 (32.6–40.3)	36.0 (33.3–38.7)	47.9 (44.6–51.1)
Low SDI vs others†	–	0.00, 1.00	25.2, <0.001	–	229.5, <0.001	343.4, <0.001

SDI – social development index, BMI – body mass index, LDL – low density lipoprotein, HDL – high density lipoprotein

*Prevalence in percent and 95% confidence intervals in parentheses.

†χ²–test statistic and p value.

largest health survey in the country, reported prevalence of smoking and obesity in urban and rural populations [36]. No other cardiometabolic risk factors were evaluated. The third cycle of this study in years 2005–2006 reported low prevalence of overweight/obesity and moderate prevalence of smoking in Indian urban and rural populations [36]. The multisite NUDS (National Urban Diabetes Survey) [37], PODIS (Prevalence of Diabetes in India Study) [38]

and INDIAB (Indian Diabetes) [39] studies were focused on diabetes prevalence. Only limited studies have evaluated multiple cardiovascular risk factors in two or more locations in India using similar methodology [40-44]. The multisite Indian Industrial Population Surveillance Study [40] reported prevalence of cardiovascular risk factors among industrial workers at eight sites in the country and reported lower prevalence of obesity, hypertension, diabe-

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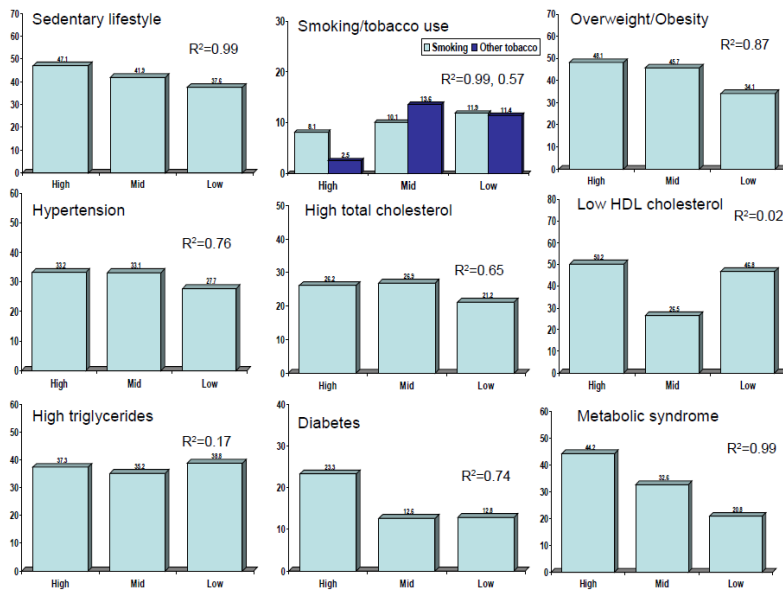
Figure 3. Prevalence of cardiometabolic risk factors in low, mid and high human social development index cities and trends (Least squares regression R2).

tes and metabolic syndrome as compared to the present study (**Table 6**). Indian Council of Medical Research Integrated Disease Surveillance Project [41] in 9 states of the country reported lower prevalence of hypertension in various rural and urban locations in the country as compared to the present study. The India Migration Study reported high prevalence of various risk factors in rural kin of industrial workers [42]. The multisite India Health Study in Mumbai, Delhi and Trivandrum focussed on diet and reported prevalence of overweight and diabetes similar to the present study [43]. Indian Women Health Study involving middle–aged women in 4 urban and 5 rural sites in India reported prevalence of cardiovascular risk factors in urban lower middle class women which were similar to the present study [44]. These studies did not comment on geo-

graphical differences. Our study is larger and more diverse than all these previous studies and shows high prevalence of multiple cardiometabolic risk factors in the middle–class Indian urban population. Although the finding of high prevalence of cardiovascular risk factors in Indian urban populations is not unique and has been reported earlier [7], the present study shows that prevalence of cardiometabolic risk factors such as metabolic syndrome, diabetes and atherogenic dyslipidemia (borderline high LDL cholesterol, high triglycerides and low HDL cholesterol) is particularly high among the urban middle–class. This finding is all the more important because large segments of Indian society are entering the middle–class and it has been predicted that within the next 30 years more than 70% of the population (more than a billion) shall be urban and most would belong to this segment of the society [20]. The INTERHEART study reported that metabolic risk factors such as atherogenic dyslipidemia (abnormal apolipoprotein A/apolipoprotein B ratio), truncal obesity, hypertension and diabetes are most important cardiovascular risk factors in South Asians [45]. Our study shows that prevalence of cardiometabolic risk factors is high in urban middle class Indian populations and predicts an impending cardiovascular epidemic in the country unless measures for risk factor control are adopted. Middle class is one of the fastest growing segment of the Indian society and is already more than 400 million subjects strong (30% of total population) [21]. Cardiovascular disease epidemic in such a large population segment would translate into heavy social as well as economic burden on the society [46]. We did not study rural locations, which currently include >60% of the Indian population, and the urban slums. This is a major study limita-

Table 6. Prevalence (%) of cardiometabolic risk factors in recent multi–centric Indian studies

Study (Year)	Sample size	Overweight/ Obesity	Hypertension	High cholesterol	Low HDL cholesterol	Diabetes	Metabolic syndrome
National Urban Diabetes Survey (2001) [37]	11 216	30.8	–	–	–	12.1	–
National Family Health Survey–3 (2005–6) [36]	198 754	12.6	–	–	–	–	–
Prevalence of Diabetes in India Study: Urban (2004) [38]	21 516	–	–	–	–	4.6	–
Prevalence of Diabetes in India Study: Rural (2004) [38]	19 754	–	–	–	–	1.9	–
Indian Industrial Population Surveillance Study (2006) [40]	10 442	31.5	27.3	–	–	9.7	28.6
Integrated Disease Surveillance Project: Urban (2009) [41]	18 552	24.1	19.9	–	–	–	–
Integrated Disease Surveillance Project: Rural (2009) [41]	19 481	9.7	14.3	–	–	–	–
India Migration Study: Rural (2010) [42]	1983	23.2	20.7	24.5	48.5	5.6	–
India Health Study (2011) [43]	3814	50.3	30.0	–	–	12.3	–
Indian Diabetes Study: Urban/Rural, 4 states (2011) [39]	13 055	–	–	–	–	5.3–13.6	–
Indian Women Health Study: Rural (2011) [44]	2616	22.5	31.5	13.5	–	4.3	–
Indian Women Health Study: Urban (2011) [44]	2008	44.6	48.2	27.7	–	15.1	–
Present study	6198	42.9	31.6	25.0	42.5	15.7	35.7

tion and our data are, therefore, not valid for the entire country and only represent the middle class (urban and possibly also the rural middle class).

Lower prevalence of cardiometabolic risk factors and greater prevalence of smoking and smokeless tobacco use in cities of eastern region of the country is an important finding (**Table 4**). This is similar to NFHS studies which reported greater prevalence of smoking and tobacco use (40% men) and lower prevalence of obesity (15%) in this region [12,13]. This geographic region also has a lower human and social development [23,25]. In the present study we have shown that human social development index, which is a composite of six social and economic factors, is an important determinant of cardiovascular risks. The study shows that apparently similar middle class locations in different cities vary in cardiovascular risk according to social and economic development of the cities. The least developed cities (Patna, Lucknow, Bikaner, **Figure 1**) which have the lowest human and social development indices (**Table 2**) have the lowest prevalence of risk factors. These cities are situated in less developed Indian states where problems of communicable diseases and maternal and child health issues are more important [47]. It is likely that once these cities progress to better social and human development indices (better education, income and occupation), cardiovascular risk factors would increase. This finding is in contrast to high income countries, where cardiovascular risk factors are more in low socioeconomic locations, neighbourhoods and states [48,49]. In many low and lower–middle income countries of Asia, Africa and South America, studies have reported findings similar to our study [1,50]. The present study, thus, suggests that populations in India have not achieved the risk factor transition associated with social and economic development where cardiovascular risk factors are greater in low socioeconomic subjects and locations as observed in Europe and North America [1,5]. The human social development index that we used is focussed on macrolevel health and social indicators which, although are indicators of economic and social deprivation (poverty), may not be directly involved in cardiovascular risks. We did not study many other social determinants of cardiovascular health [5] which are equally important risk factors.

Strengths and limitations

The present study, thus, provides a new insight into the cardiovascular disease epidemic in India. We have highlighted the high prevalence of cardiometabolic risk factors in urban locations in the country. This study also shows importance of poverty decline (social development) as driver of cardiovascular risk. Other strengths of the study include inclusion of almost all the regions of the country; evaluation of risk factors in urban locations that are known
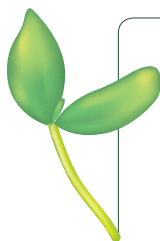
to have high cardiovascular disease incidence and prevalence, and use of uniform methodology and measurements, especially biochemical measurements.

Limitations of the study include non–inclusion of large Indian states such as Andhra Pradesh and Madhya Pradesh, but inclusion of locations in other large states such as Uttar Pradesh, Bihar, Rajasthan and Maharashtra is unique to this study. Second, sampling confined to urban locations in middle–level cities could be criticised for selection bias but such urban locations now represent the heart of India [51] and are fertile ground for cardiovascular epidemic. Moreover, rapidly increasing urbanization in the country shall lead to more than 60% of the 1.5 billion subjects living in similar locations within the next 30 years [20,21,51] and there is a need to create more healthy cities focused on social, biological and built environment [18]. Third, the sample size at individual site is too small to identify differences in risk factors. We, therefore, combined cities of a particular geographic region or with similar social development index to determine regional difference in prevalence of various cardiovascular risk factors. Fourthly, sampling confined to middle–class locations in urban areas may not be representative of the city where almost 30% subjects live in slums or in India where more than 65% live in rural locations [47]. However, as mentioned above, the study was focused on middle–level cities and middle–class locations where more than 300 million Indians live [20]. Fifthly, the definition of middle class could vary from state to state and this is a study imitation. We used the criteria adopted by the state governments to classify middle class locations as mentioned earlier. This could lead to non–uniform characterisation of the middle class in the cities. However, as observed in **Table 2**, the sociodemographic pattern of cities in almost uniform. Moreover, we grouped the cities into tertiles of high, middle and low social development index which has resulted in grouping of similar cities with better representativeness. Sixthly, selection of cities, locations and participants could be criticised as biased due to convenience sampling. The best epidemiological approach would have been to divide the cities in the whole country depending on high, middle and low socioeconomic development and randomly select a few, randomly select middle–class locations in individual cities and then randomly select specific areas within the locations and then assess the risk factors in these locations based on either random enumeration of households or a consecutive sampling as done in the present study. We did not randomise the whole cities into strata based on locations and amenities but chose middle class locations, as classified by government records, and then performed the consecutive household survey or simple cluster sampling at all the 11 locations. This method has been recommended by the WHO as alternate strategy to stratified random sampling.[26] Seventhly, the study has

low response rates (62%) which is an important limitation. However, the response rate is similar to many previous studies from India.[7] It has been opined that response rate of >60% be considered as threshold of acceptability and has face validity as a measure of survey quality [52]. Empirical assessments over the past decade have concluded that the response rate of a survey may not be as strongly associated with the quality of representativeness of the survey as is generally believed. We do not have characteristics of non–responders but neighbourhoods were similar to subjects in the present study. And finally, we have linked individual level outcomes with macro–level predictors (social development index) in the present study and this may be considered a study limitation. However, we believe that study of macro–level predictors of cardiovascular health is important because only limited studies exist from low income countries that have evaluated such associations and also because these determinants are more amenable to social engineering [18].

In conclusion, this multisite cardiovascular risk factor study in India shows that as cities move away from economic and social deprivation there is greater prevalence of obesity, metabolic syndrome, diabetes and dyslipidemias. Behavioural risk factors such as smoking, smokeless tobacco use, low fruits and vegetables intake and high visible fat intake are higher in low social development cities. This indicates that Indian urban populations are in different stages of epidemiological and chronic disease transition– low social development cities have greater prevalence of behavioural risk factors while more developed cities have greater cardiometabolic risk factors. This mixed picture of risk factor transition suggests that the cardiovascular epidemic is still evolving in India, similar to many lower–middle income countries of Europe, Asia, South America and Africa [53]. This study, thus, shows that decline in cardiovascular risks that occurs with social and human development has not yet occurred in India. Studies in developed countries have reported that socioeconomic tansition (captured by social development index in the present study) is inversely associated with cardiometabolic risks and greater social and human development index is associated with lower risks [4,5,53]. Our study shows that in India the regional variations in cardiovascular risk factors related to geography (greater prevalence in eastern India) is related to lower social and human development of this region. This study, therefore, suggests that in India there is need to focus on macrolevel social determinants of cardiovascular risks to control the cardiovascular epidemic. These findings are all the more important in context of WHO 25x25 initiative, 25% reduction in mortality from noncommunicable diseases by the year 2025 [50]. National health policy of India, and many low and low–middle income countries, should be directed to not only improving macrolevel societal factors– amelioration of poverty, inequity, illiteracy, unemployment and undernutrition– that impact health, but also promotion of cardiovascular health with standard public health approaches [1,50]. The most cost–effective approach to cardiovascular disease control are implementation of policy measures highlighted by WHO [50] to attain the nine global noncommunicable disease targets, all of which are focussed on cardiovascular diseases.

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Causes of accidental childhood deaths in China in 2010: A systematic review and analysis

Kit Yee Chan[1,2], Xin–wei Yu[3],
Jia–peng Lu[3], Alessandro Rhyll
Demaio[4,5], Kirsty Bowman[1], Evropi
Theodoratou[1]

[1] The University of Edinburgh Medical School, Edinburgh, Scotland, UK

[2] Nossal Institute for Global Health, Melbourne School of Population and Global Health, University of Melbourne. Melbourne, Australia

[3] Municipal Key Laboratory of Clinical Epidemiology, School of Public Health, Capital Medical University, Beijing, China

[4] Harvard Global Equity Initiative, Harvard Medical School, Cambridge, MA, USA

[5] Copenhagen School of Global Health, University of Copenhagen, Copenhagen, Denmark

Correspondence to:

Dr Evropi Theodoratou
Centre for Population Health Sciences
The University of Edinburgh Medical School
Teviot Place, Edinburgh EH8 9AG
Scotland, UK
e.theodoratou@ed.ac.uk

Background Infectious causes of childhood deaths in the world have decreased substantially in the 21st century. This trend has exposed accidental deaths as an increasingly important future challenge. Presently, little is known about the cause structure of accidental childhood deaths in low– and middle–income country (LMIC) settings. In this paper, we aim to establish cause structure for accidental deaths in children aged 0–4 years in China in the year 2010.

Methods In this paper, we explored the database of 208 multi–cause child mortality studies in Chinese that formed a basis for the first published estimate of the causes of child deaths in China (for the year 2008). Only five of those studies identified specific causes of accidental deaths. Because of this, we searched the Chinese medical literature databases CNKI and WanFang for single–cause mortality studies that were focused on accidental deaths. We identified 71 further studies that provided specific causes for accidental deaths. We used epidemiological modeling to estimate the number of accidental child deaths in China in 2010 and to assign those deaths to specific causes.

Results In 2010, we estimated 314 581 deaths in children 0–4 years in China, of which 31 633 (10.1%) were accidental. Accidental deaths contributed 7240 (4.0%) of all deaths in neonatal period, 8838 (10.5%) among all post–neonatal infant deaths, and 15 554 (31.7%) among children with 1–4 years of age. Among four tested models, the most predictive was used to establish the likely cause structure of accidental deaths in China. We estimated that asphyxia caused 9490 (95% confidence interval (CI) 8224–11 072), drowning 5694 (95% CI 5061–6327), traffic accidents 3796 (95% CI 3163–4745), poisoning 3163 (95% CI 2531–3796) and falls 2531 (95% CI 2214–3163) deaths. Based on medians from a few rare studies, we also predict 633 (95% CI 316–1265) deaths to be due to burns and 316 (95% CI 0–633) due to falling objects. Together, these 7 causes explain more than 80% of all accidental deaths when modeling is primarily used, and more than 95% when the analysis is based purely on medians from the 76 available studies.

Conclusions Reduction in global child mortality is a leading political priority and accidental deaths will soon emerge as one of the main challenges. In this paper we provided a detailed breakdown of causes of these deaths in a large middle–income country. We noted that, wherever the share of accidental deaths among all child deaths is increased, drowning is more likely to be the leading cause; asphyxia seems to be equally important in all contexts, while traffic accidents, poisoning and falls are relatively more important in contexts where the overall share of accidents to all child deaths is low.

Infectious causes of childhood deaths in the world have decreased substantially in the 21st century [1]. The World Health Organization (WHO), UNICEF and Child Health Epidemiology Reference Group (CHERG) estimated that the number of child deaths globally decreased from about 10.8 million in the year 2000 to about 7.6 million in the year 2010 and the majority of the reduction is attributable to fewer deaths from common childhood infections, such as pneumonia and diarrhoea [2,3]. This trend has exposed accidental deaths as an increasingly important future challenge. In 2000 accidents were estimated to contribute 3% to the total number of child deaths globally and in 2010 this increased to 5% [2,3]. In China, as perhaps the best example of a large middle–income country, these trends were even more pronounced. The child mortality decreased by nearly 75% between 2000 and 2010 and CHERG estimated that the proportion of accidental deaths in China increased from 9% to 11% during the same period [4]. To address the emerging challenge of childhood accidental deaths, more information is required on the specific causes and patterns of their occurrence in different contexts. Presently, little is known about the cause structure of accidental childhood deaths in low– and middle–income country (LMIC) settings.

In 2008, the WHO estimated up to 950 000 fatalities from injuries for children aged 0–18 years globally [5]. In the same year, WHO and UNICEF published their landmark *World report on child injury prevention* [6]. It was estimated that some 90% of these deaths were attributable to unintentional injuries [5] and that 95% of injury–related deaths in children occurred in LMIC [5,6]. The recent WHO's *World Health Statistics 2013* shows that the percentage distribution of injuries for the under five mortality has increased across all sub–categories by age and income from 2000 to 2010 [5-7]. However, information on fatal injuries from LMIC is often derived from medical facilities, thus underestimating the population–based burden [8]. This problem is made worse because definitions for injury mechanisms have not been uniform across different study settings. They can particularly vary with regards to drowning, burns, poisonings, and what is defined as "other unintentional injuries" [9–11].

There is persisting uncertainty over the estimates of accidental child deaths globally. In many low- and middle-income regions, accidents are relatively rare among other causes of child deaths, contributing only several percents. This makes them prone to greater over– or under–estimation in multi–cause models, such as those used by CHERG, in comparison to the more frequent causes of death. Recently, an increased number of single–cause studies focused on accidents as causes of deaths in developing countries have been published, which is especially true for China. Previous results from a multi–cause model from China

have already suggested a possible under–estimation of accidents and injuries as a cause of child deaths globally [4]. Better understanding of specific cause composition of accidental childhood deaths would reaffirm previous reports and assist in developing strategies and policies that could prevent these deaths in different LMIC contexts.

This study has four aims: (1) To estimate the total number of accidental deaths in children under five years in 2010 among neonates, post–neonatal infants, and children aged 1–4 years in all Chinese provinces; (2) to estimate the relative contribution of accidents to all child deaths in each of these age groups; (3) to define a specific cause to all accidental childhood deaths in China; and (4) to investigate if there are any significant context–related predictors of the proportional contribution of specific causes to the overall number of deaths due to accidents.

METHODS

In terms of methods, this study is an extension of our previous study on the causes of child deaths in China in 2008, where a systematic review of in Chinese literature was performed and then followed by epidemiological modeling [4]. In that study, we identified 206 multi–cause studies published between 2000 and 2008 that contributed information on a very large number of childhood deaths (about 350 000 in total) that had an exact cause assigned. That information allowed us to develop models that related the proportional contribution of each major cause of child deaths to the underlying context–specific under–five mortality rate (U5MR) [4]. If the U5MR for the whole of China is known, then the same models can be applied to estimate the proportional contribution of different causes to all child deaths in China in any given calendar year for which U5MR is available. Moreover, if the number of livebirths is also available for the same calendar year of interest, then the U5MR and proportions attributable to different causes can be translated into absolute number of deaths due to each cause [4].

To address *the first aim* of this study – ie, to estimate the total number of accidental deaths in children under five years of age in China in 2010 among neonates, post–neonatal infants, and children aged 1–4 years in all Chinese provinces – we needed to obtain the U5MR for China in the year 2010. This was available from the CHERG national–level estimate of the causes of child deaths for the year 2010 [3]. Using the same models as in our previous paper on the causes of child deaths in China in 2008, we estimated the proportional cause contribution in the year 2010 by province and 3 major age groups: neonates (0–28 days), post–neonatal infants (1–11 months), and children aged 1–4 years. We presented the results in **Table 1,** showing

the distribution for all deaths and specifically for accidental deaths.

To achieve *the second aim* – ie, to estimate the relative contribution of accidents to all child deaths in each of these age groups, we simply applied all previously developed models [4] to the number of livebirths in China in 2010 and U5MR in 2010, both of them provided from the same sources as in the previous study [1,3,12,13]. We then divided the total number of estimated accidental deaths by the total number of deaths due to all causes in 3 major age groups: neonates (0–28 days), post–neonatal infants (1–11 months), and children aged 1–4 years. We also performed these calculations for the whole period 0–4 years and presented the results in **Table 1**.

To achieve *the third aim* – to define a specific cause to all accidental childhood deaths in China – we required addi-

tional information on the specific causes of accidental deaths, which we did not acquire in our previous study on the causes of child deaths in China [4]. To obtain this information, we first reviewed all 206 multi–cause studies published 2000–2008 to identify those that reported accidents as causes of child deaths and we identified 106 such studies. Then, we reviewed those studies for a more specific breakdown of causes of such deaths, but only 5 of 106 studies provided this information. This necessitated a new review of the literature in search of single–cause studies on accidental childhood deaths that provided a detailed breakdown by cause. We repeated the search of the literature using the same procedure as in our previous paper [4], with the only difference that we added the search terms "accidents" and/or "injuries". This allowed us to identify 71 further studies, nearly all of them from CNKI and Wan Fang databases. Adding the five multi–cause studies from the

Table 1. Child Health Epidemiology Reference Group (CHERG) estimates of the number of deaths in China in the year 2010 by province among neonates, post–neonatal infants, children aged 1–4 years and 0–4 years (columns 2–5) and the number of those deaths attributable to accidents (columns 6–9)*

Province	TOTAL NUMBER OF DEATHS IN EACH PROVINCE BY AGE GROUP				NUMBER OF ACCIDENTAL DEATHS IN EACH PROVINCE BY AGE GROUP			
	Neonatal	1 month – 1 year	1–4 years	Total	Neonatal	1 month – 1 year	1–4 years	Total
Anhui	10 165	4638	2771	17 574	407	500	880	1787
Beijing	370	97	118	585	15	16	45	75
Chongqing	3100	1256	880	5235	124	149	293	566
Fujian	3715	1422	1074	6212	149	176	365	690
Gansu	3589	1610	984	6183	144	176	315	634
Guangdong	6636	2097	2025	10 757	265	298	731	1295
Guangxi Zhuang AR	10 098	4569	2761	17 428	404	496	880	1780
Guizhou	12 927	7504	3197	23 628	517	650	908	2076
Hainan	1703	791	461	2955	68	84	145	298
Hebei	13 542	6418	3640	23 600	542	670	1138	2349
Heilongjiang	4673	2343	1229	8245	187	233	375	795
Henan	9090	3234	2685	15 009	364	423	935	1721
Hubei	5311	2145	1509	8965	212	255	503	970
Hunan	7487	3024	2128	12 639	299	360	709	1368
Jiangsu	4109	1246	1266	6621	164	182	463	809
Jiangxi	9304	4463	2489	16 256	372	461	774	1607
Jilin	1119	327	348	1794	45	49	129	222
Liaoning	2530	924	742	4195	101	119	256	476
Neimenggu (Inner Mongolia) AR	2703	1223	739	4666	108	133	236	476
Ningxia Hui AR	1475	744	387	2606	59	74	118	250
Qinghai	1278	607	343	2228	51	63	107	222
Shaanxi (Qin)	6049	3165	1564	10 778	242	303	468	1012
Shandong	8913	3485	2560	14 958	357	425	863	1644
Shanghai	275	61	91	426	11	11	36	58
Shanxi (Jin)	5608	2726	1493	9828	224	278	461	964
Sichuan	24 624	14 329	6083	45 035	985	1238	1726	3950
Tianjin	360	92	115	567	14	15	44	73
Xinjiang Wei AR	7701	4189	1959	13 848	308	386	575	1269
Xizang (Tibet) AR	809	430	208	1447	32	41	62	135
Yunnan	8480	4169	2248	14 897	339	422	691	1452
Zhejiang	3256	1209	950	5414	130	153	326	609
Age–specific total for China	180 998	84 535	49 048	314 581	7240	8838	15 554	31 633
% of total for China	100.0%	100.0%	100.0%	100.0%	4.0%	10.5%	31.7%	10.1%

*These CHERG estimates [3] are based on models for China for the year 2008 that were explained in detail by Rudan et al. [4].

original review [4], this allowed us to reach a total of 76 studies with useful information. Among them, 67 reported drowning and asphyxia as specific causes, 66 reported traffic accidents, 61 reported falls, 50 reported at least one death due to poisoning, 11 reported burns and 4 reported falling objects. All other causes were sporadic and mentioned only as a rare observation in a single study. From all 76 studies it was possible to compute proportional contributions of these causes to all accidental deaths. For each specific cause we presented median proportion, inter–quartile range (IQR) and maximum and minimum observed percentage in a box–and–whiskers plot in **Figure 1**.

Finally, *the fourth aim* of our study was to investigate if there are any significant context–related predictors of the proportional contribution of specific causes to the overall number of deaths due to accidents. This aim should inform us whether we can predict the proportional contribution of different specific causes if we have other information about the context. We could specify three different predictors that were available at the provincial level: (i) overall U5MR; (ii) U5MR that is due to all accidental deaths; and (iii) proportional contribution of accidental deaths to all deaths in each province. We used regression analysis and three separate models to explore whether any of these three predictor variables are significantly associated with proportion of any specific cause in all accidental deaths. We also added the fourth model, where we used multivariate design to account for all three predictors at the same time. We used those four models to predict the proportional contribution of the five specific causes with sufficient information available: drowning, asphyxia, traffic accidents, falls and poisoning. In performing these analyses, we followed all procedures as detailed in our previous paper [4]. We presented a summary of the four models applied to five specific causes of accidental deaths in **Table 2** and **Figures 2** to **6**.
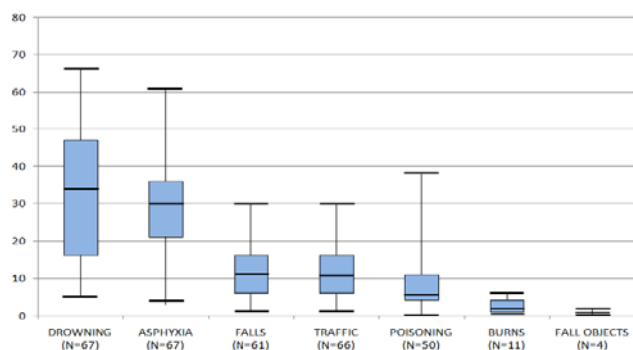
Figure 1. Box and whiskers plot of the proportions (Y–axis) of accidental childhood deaths in China in 2010 by specific causes (X–axis): medians, inter–quartile ranges, maximum and minimum value observed in the studies that provided adequate information. The number of studies available for each cause ranged from 4 to 67 and is presented below X–axis.

Having completed the analyses towards the third and the fourth aim, it was possible to predict the absolute number of accidental deaths due to each of the specific causes in China in 2010 in two main ways: (i) using median proportional contributions and IQRs from all available studies and applying them to estimates of all accidental deaths in China; or (ii) using the model that explained the largest proportion of variance and applying it to the entire Chinese population. We presented a comparison of these two approaches in **Table 3**.

RESULTS

Our paper presented the time series with the proportional contribution of major causes of child deaths in China from 2000–2008 [4]. Using the same methods and applying the U5MR and the number of livebirths for the year 2010 for China [3,4,12,13] we arrived to the estimates presented in **Table 1**. There were 314 581 deaths in children aged 0–4 years in China in 2010, and we estimated that 31 633

Table 2. A summary of results of epidemiological modeling: association between proportion of deaths due to each specific accidental cause (criterion variable) and four different predictor variables

| Model	Coefficient (β)	Adjusted R²
Cause of death: drowning (n = 67 studies)		
ln (U5MR)	0.05	–0.01
ln (U5AMR)	0.25	0.10
ln (%ACC in total)	0.95	0.36
ln (all three predictors)	–0.81	0.35
Cause of death: asphyxia (n = 67 studies)		
ln (U5MR)	0.006	–0.015
ln (U5AMR)	–0.02	–0.013
ln (%ACC in total)	–0.11	–0.002
ln (all three predictors)	0.35	–0.03
Cause of death: falls (n = 61 studies)		
ln (U5MR)	–0.12	0.01
ln (U5AMR)	–0.24	0.14
ln (%ACC in total)	–0.59	0.23
ln (all three predictors)	1.39	0.24
Cause of death: traffic accidents (n = 67 studies)		
ln (U5MR)	–0.43	0.24
ln (U5AMR)	–0.43	0.34
ln (%ACC in total)	–0.49	0.10
ln (all three predictors)	–1.02	0.32
Cause of death: poisoning (n = 50 studies)		
ln (U5MR)	–0.05	–0.02
ln (U5AMR)	–0.29	0.10
ln (%ACC in total)	–1.01	0.37
ln (all three predictors)	0.03	0.34

U5MR – under–five mortality rate (all deaths included) reported in each study, U5AMR – under–five mortality rate based on accidental deaths reported in each study, %ACC in total – the proportion of accidental deaths in all deaths in each study, β – regression coefficient, R² – the proportion of variance in the criterion variable explained by each predictor variable
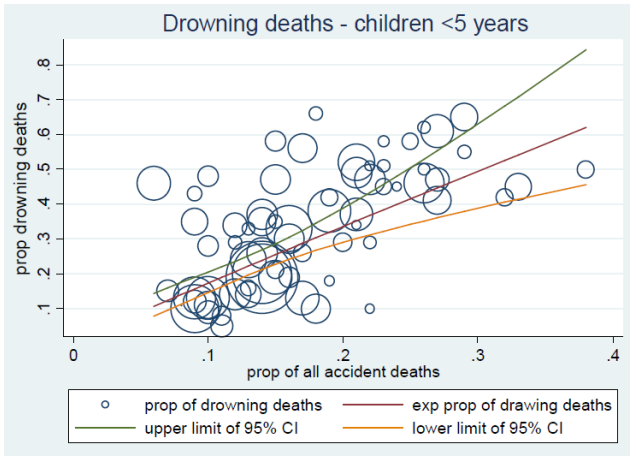
Figure 2. Epidemiological modeling of the association between the most significant predictor variable (proportion of accidental deaths in all child deaths in each study; X–axis) and criterion variable (proportion of deaths caused by drowning in all accidental deaths; Y–axis). Data points represent studies with available information and the size of the "bubbles" is proportional to the total number of child deaths observed in each study. The regression line with upper and lower limit of 95% confidence interval is shown across the range of data.
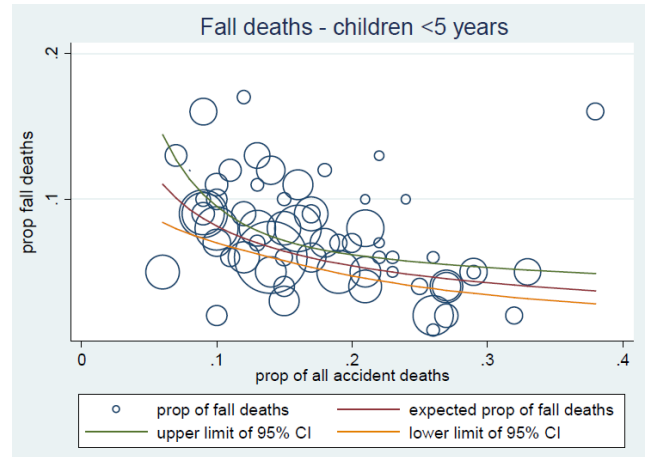
Figure 4. Epidemiological modeling of the association between the most significant predictor variable (proportion of accidental deaths in all child deaths in each study; X–axis) and criterion variable (proportion of deaths caused by falls in all accidental deaths; Y–axis). Data points represent studies with available information and the size of the "bubbles" is proportional to the total number of child deaths observed in each study. The regression line with upper and lower limit of 95% confidence interval is shown across the range of data.
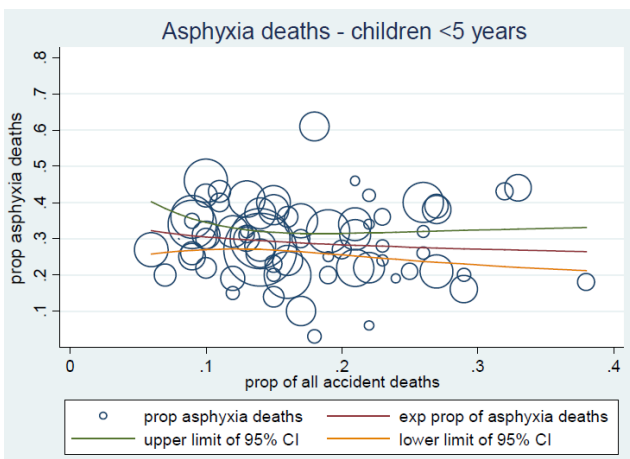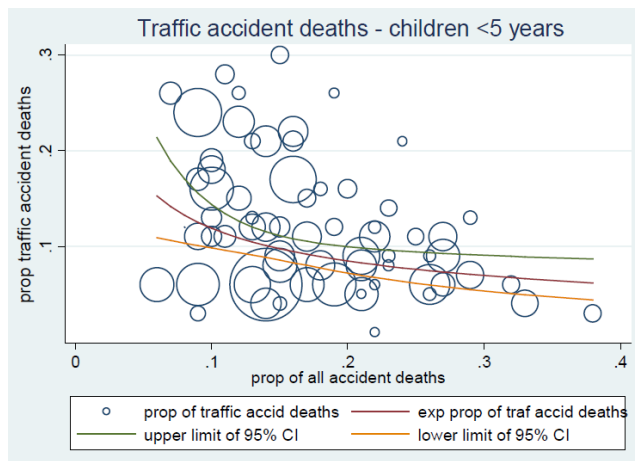

Figure 3. Epidemiological modeling of the association between the most significant predictor variable (proportion of accidental deaths in all child deaths in each study; X–axis) and criterion variable (proportion of deaths caused by asphyxia in all accidental deaths; Y–axis). Data points represent studies with available information and the size of the "bubbles" is proportional to the total number of child deaths observed in each study. The regression line with upper and lower limit of 95% confidence interval is shown across the range of data.

(10.1%) were due to accidents and injuries. There were 7240 deaths in neonates (4.0% of all neonatal deaths), 8838 deaths in post–neonatal infants (10.5% of all post–neonatal infant deaths) and 15 554 deaths in children 1–4 years (31.7% of all deaths in 1–4 years). This analysis addressed the first and second aim of this study.

Figure 1 shows the box and whiskers plot of the proportions (Y–axis) of accidental childhood deaths in China in 2010 by specific causes (X–axis): medians, inter–quartile ranges (IQR), maximum and minimum value observed in the studies that provided adequate information. The number of studies available for each cause ranged from 4 to 67. Based on medians and IQR, drowning was the leading specific cause with 34% (IQR 17–47%) of all accidental deaths, followed by asphyxia (30%; IQR 21–36%), falls (11%; IQR 6–16%), traffic accidents (11%; IQR 6–16%), poisoning (6%; IQR 4–11%), burns (2%; IQR 1–4%) and falling objects (1%; IQR 0–2%). Applied to the total number of accidental deaths (31 633), this translates into 10755 (5378–14 867) deaths attributable to drowning, 9490 (6643–11 388) to asphyxia, 3480 (1898–5061) to falls, 3480 (1898–5061) to traffic accidents, 1898 (1265–3480) to poisoning, 633 (316–1265) to burns and 316 (0–633) to falling objects. This analysis addressed the third aim of the study.

We then tried to learn more from the information available in the 76 studies. We were interested in whether any context–specific variables may accurately predict the distribution of specific causes. From each study, we extracted three predictors that were universally available: local U5MR due to all child deaths, local U5MR that was attributable to accidental deaths only, and the ratio between the latter and the former, ie, the proportional contribution of accidental deaths to all child deaths. We also developed a model that took into account all three variables. These variables were useful, because they were readily available for all provinces

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Figure 5. Epidemiological modeling of the association between the most significant predictor variable (proportion of accidental deaths in all child deaths in each study; X–axis) and criterion variable (proportion of deaths caused by traffic accidents in all accidental deaths; Y–axis). Data points represent studies with available information and the size of the "bubbles" is proportional to the total number of child deaths observed in each study. The regression line with upper and lower limit of 95% confidence interval is shown across the range of data.
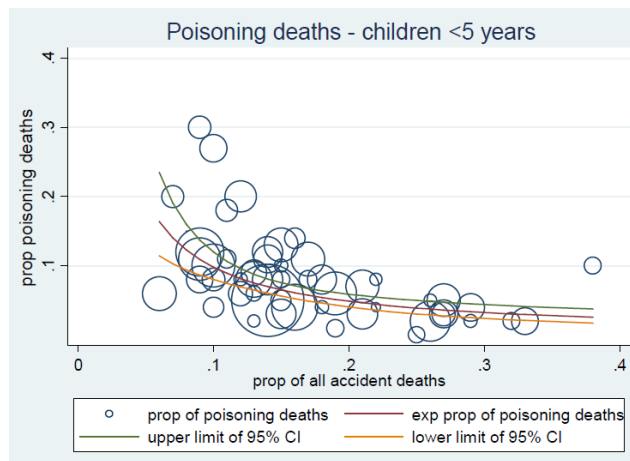
Figure 6. Epidemiological modeling of the association between the most significant predictor variable (proportion of accidental deaths in all child deaths in each study; X–axis) and criterion variable (proportion of deaths caused by poisoning in all accidental deaths; Y–axis). Data points represent studies with available information and the size of the "bubbles" is proportional to the total number of child deaths observed in each study. The regression line with upper and lower limit of 95% confidence interval is shown across the range of data.

and for China as a whole. **Table 2** presents a summary of results of epidemiological modeling, in which association between proportion of deaths due to each specific accidental cause (criterion variable) and four different predictor variables was explored. It was clear that the third model, based on the ratio between U5MR due to accidents and U5MR due to all deaths, was generally the most predictive. In **Figures 2** to **6**, we present the association between this predictor and the proportion of accidental deaths due to drowning, asphyxia, traffic accidents, falls and poisoning. Data points in these figures represent studies with available information and the size of "bubbles" is proportional to the total number of child deaths observed in each study. The regression line with upper and lower limit of 95% confidence interval is shown across the range of data.

We then applied these models to the entire population of China. This implicated asphyxia as the leading cause of ac-

cidental deaths in China in 2010, with 9490 deaths (95% CI 8224–11072), followed by drowning (5694 deaths; 95% CI 5061–6327), traffic accidents (3796 deaths; 95% CI 3163–4745), poisoning (3163 deaths; 95% CI 2531–3796) and falls (2531 deaths; 95% CI 2214–3163). Together, these 5 causes explain about 80% of all accidental deaths when modeling is primarily used, while the seven causes with available medians explain more than 95% when the analysis is based purely on medians from the 76 available studies.

Table 3 shows the differences between two sets of estimates when the two approaches are used. When modeling is used instead of medians, the role of asphyxia and traffic accidents is largely unchanged. However, drowning is revised sharply downwards, although remaining the second most important cause. Falls are also revised downwards, while poisoning is revised upwards.

Table 3. Estimates of the number of child deaths in China in 2010 attributable to different causes of accidental deaths*

CAUSES OF ACCIDENTAL DEATH IN CHILDREN AGED 0–4 YEARS IN CHINA IN 2010	BASED ON MEDIAN (WITH IQR)	No. (DEATHS)	BASED ON MODEL (WITH 95% CI)	No. (DEATHS)
All accidental deaths	100%	31633	100%	31633
Drowning (n=67 studies)	34% (17–47%)	10755 (5378–14867)	18% (16–20%)	5694 (5061–6327)
Asphyxia (n=67 studies)	30% (21–36%)	9490 (6643–11388)	30% (26–35%)	9490 (8224–11072)
Falls (n=61 studies)	11% (6–16%)	3480 (1898–5061)	8% (7–10%)	2531 (2214–3163)
Traffic accidents (n=66 studies)	11% (6–16%)	3480 (1898–5061)	12% (10–15%)	3796 (3163–4745)
Poisoning (n=50 studies)	6% (4–11%)	1898 (1265–3480)	10% (8–12%)	3163 (2531–3796)
Burns (n=11 studies)	2% (1–4%)	633 (316–1265)	N/A	N/A
Falling objects (n=4 studies)	1% (0–2%)	316 (0–633)	N/A	N/A

IQR – interquartile range, CI – confidence interval, N/A – not applicable

*The estimates are based on the number of studies that varied between 4 (for falling objects) and 67 (for drowning and asphyxia). The estimates are derived from medians and inter–quartile ranges (column 2–3) and from epidemiological models with the highest proportion of variance explained and 95% confidence intervals (column 4–5).

DISCUSSION

Reduction in global child mortality is a leading political priority and accidental deaths will soon emerge as one of the main challenges. In this paper we provided a detailed breakdown of causes of accidental deaths in a large middle–income country. An important finding of our study is that, wherever the share of accidental deaths among all child deaths is high, drowning is more likely to be the leading cause; asphyxia seems to be equally important in all contexts, while traffic accidents, poisoning and falls are relatively more important in contexts where the overall share of accidents to all child deaths is low. There are differences in estimates based on medians and modeling. This may be explained by a predominance of studies from the areas in which the proportion of accidental deaths in all child deaths is high. It is not surprising that such contexts would attract more studies, and our analyses showed that this would favor drowning over other causes. This is why we believe that the estimates based on modeling are more accurate and robust. We recommend that the estimates based on modeling are considered as the more relevant ones for the whole China.

Knowledge on magnitude is the first step in the public health approach towards reducing the number of deaths from childhood accidents and unintentional injuries [14]. Without this baseline data at the national level on the profile of specific causes in children, awareness of the problem will be very limited, hindering the development of national policies [15]. Injury prevention policies are crucial for guiding preventative efforts to reduce deaths from unintentional injuries [16]. Estimating the mortality burden from accidents and injuries for children aged less than five years can highlight areas that need to be improved to generate the relevant information for policy formulation. Funding and attention in the area of unintentional injuries has not been equivalent to that of communicable and non–communicable diseases [9]. It was estimated that in the period between 2006–2007 only 1% of the WHO's budget and an additional 1% from other sources were provided for the field of injury control and prevention [17]. Perceptions that unintentional injuries cannot be avoided also need to be challenged [18]. Interventions that have been tracked to monitor progress towards MDG4 and MDG 5 have also neglected interventions that focused on reducing preventable deaths from injuries [3,8].

Aggregating mortality data for low and middle–income countries can increase the awareness of the number of deaths caused by unintentional injuries. However, as highlighted in this study, there is a lack of country level data that underpins mortality estimates. Individual countries, and even areas within a country, can differ with regards to the leading mechanisms causing unintentional injuries, as exemplified by the range of mortality rates presented in this review [11]. For countries signatory to the Convention on the Rights of the Child, it is essential that there is greater awareness of the burden caused by unintentional injuries and focus on its redress [19]. Low and middle–income countries need to use a wide range of low cost already established information systems to collate mortality data for unintentional injuries [14,20]. Suggestions have been made that in countries where mortuaries are used to store bodies, this could be a source of injury data [20]. For instance in the year 1996 in Kumasi, Ghana, improvements were made through training of the nurses to help aid with the accurate recording of the mechanism of injury and the body region affected [15]. A review in 2006 of this mortuary showed that reporting was still high even after funding had ceased, and additional unintentional mechanisms had begun to be collected and reported [21]. Previously established demographic surveillance sites could also be used to collect data on mortalities due to injuries. Community based studies are needed to supplement these sources of data as not all deaths will reach the mortuary or be included in a surveillance sites [22,23].
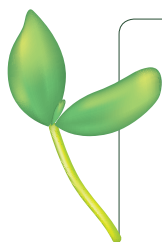
Moreover, improvements need to be made with the reporting of coding that has been used to determine unintentional deaths. Separation of mechanisms that are sometimes placed into the category of 'other unintentional' deaths is required to allow within and country comparisons [20]. Some authors suggest that adherence to a strict division between intentional and unintentional accidents and injuries may result in common risk factors being missed [24]. In China, there seems to be a reasonably uniform system of accidents and injuries which is being used to attribute the specific cause of deaths in single–cause studies, but that system does not always easily translate into ICD–10 classification, or in classification used in other countries. There is uncertainty over the deaths caused by asphyxia in China, which seem to cause a large proportion of all deaths and it is possible that they therefore include SIDS – "*sudden infant death syndrome*". However, it was not possible to learn more about this important issue from the studies themselves and further work would be needed to disentangle and characterize this category. Other categories – such as drowning, traffic accidents, falls, poisoning, burns and falling objects – are much easier to translate to other classifications.

Some middle–income countries, such as Viet Nam, have already moved towards tackling childhood unintentional injuries systematically, though specific policies. The establishment of a National Policy on Injury Prevention has resulted in an increased awareness to the problem of unintentional injuries in children in Viet Nam and has given some direction for preventative efforts [25]. Educational campaigns, swimming lessons, legislation and enforcement of helmet

wearing for the population aged over 6 years and creating safer homes, schools and community environments have all been implemented to some degree throughout the country [25]. Further improvements need to be achieved in terms of enforcing current legislations, and extending the helmet legislation to those aged less than 6 years, and information systems for collecting mortality data [25]. We believe that China is very well suited to follow and make further important progress in the reduction of child mortality – which has been the most striking and successful among all the low– and middle–income countries over the past two decades.

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Social autopsy study identifies determinants of neonatal mortality in Doume, Nguelemendouka and Abong–Mbang health districts, Eastern Region of Cameroon

Alain K. Koffi[1], Paul–Roger Libite[2],
Seidou Moluh[3], Romain Wounang[2],
Henry D. Kalter[1]

[1] Department of International Health, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD, USA
[2] National Institute of Statistics, Yaoundé, Cameroon
[3] Ministry of Health, Yaoundé, Cameroon

Background Reducing preventable medical causes of neonatal death for faster progress toward the MGD4 will require Cameroon to adequately address the social factors contributing to these deaths. The objective of this paper is to explore the social, behavioral and health systems determinants of newborn death in Doume, Nguelemendouka and Abong–Mbang health districts, in Eastern Region of Cameroon, from 2007–2010.

Methods Data come from the 2012 Verbal/Social Autopsy (VASA) study, which aimed to determine the biological causes and social, behavioral and health systems determinants of under–five deaths in Doume, Nguelemendouka and Abong–Mbang health districts in Eastern Region of Cameroon. The analysis of the data was guided by the review of the coverage of key interventions along the continuum of normal maternal and newborn care and by the description of breakdowns in the care provided for severe neonatal illnesses within the Pathway to Survival conceptual framework.

Results One hundred sixty–four newborn deaths were confirmed from the VASA survey. The majority of the deceased newborns were living in households with poor socio–economic conditions. Most (60–80%) neonates were born to mothers who had one or more pregnancy or labor and delivery complications. Only 23% of the deceased newborns benefited from hygienic cord care after birth. Half received appropriate thermal care and only 6% were breastfed within one hour after birth. Sixty percent of the deaths occurred during the first day of life. Fifty–five percent of the babies were born at home. More than half of the deaths (57%) occurred at home. Of the 64 neonates born at a health facility, about 63% died in the health facility without leaving. Careseeking was delayed for several neonates who became sick after the first week of life and whose illnesses were less serious at the onset until they became more severely ill. Cost, including for transport, health care and other expenses, emerged as main barriers to formal care–seeking both for the mothers and their newborns.

Conclusions This study presents an opportunity to strengthen maternal and newborn health by increasing the coverage of essential and low cost interventions that could have saved the lives of many newborns in eastern Cameroon.

Correspondence to:

Alain K. Koffi
Department of International Health
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St., Room E8610
Baltimore, MD, 21205, USA
akoffi1@jhu.edu

Progress in reducing global child mortality since 1990 has been encouraging. Yet, reductions in neonatal mortality lag behind survival gains among older children: neonatal deaths accounted for about 44% of 6.3 million under–five deaths in 2013 [1]. There is a global consensus that to achieve the Millennium Development Goal for child survival (MDG–4) to reduce mortality of children under–five years of age by two–thirds between 1990 and 2015, neonatal deaths need to be substantially reduced [2,3].

With an estimated under–five mortality rate in 2012 of 95 deaths per 1000 live births, Cameroon has the 21st highest child mortality rate in the world; neonatal mortality contributed about 30% of these deaths. While neonatal mortality decreased by 20%, from 35 to 28, from 1990 to 2012 [4], the fact that most deaths were from preventable causes suggests that greater attention and investment is required to address neonatal deaths.

In Cameroon, as in many Sub–Saharan African countries, most neonatal deaths occur at home, outside of a medical setting, and are neither registered nor certified as to the cause of death [5]. In addition, data are lacking on the household, community and health system determinants that contribute to these deaths. Making faster progress toward the MGD–4 by reducing preventable causes of deaths will require the country to identify and address these factors contributing to neonatal deaths.

Previous studies have described social factors or determinants that influence neonatal mortality. These factors include poor recognition and understanding of illness signs; socio–cultural traditions regarding maternal and newborn seclusion; lack of access to care due to distance to a facility or provider, lack of transportation means, and limited financial resources for health care or transport; poor quality of care at facilities; and the opportunity costs of missed work or childcare [6–8].

Recently there has been a growing demand for a framework that organizes these factors and a tool to describe them. [9,10]. Two conceptual frameworks, the Pathway to Survival [11] and the Three Delays model [10,12] have been found useful to organize and guide the analysis of these data. In a nutshell, the Pathway to Survival identifies and organizes social, cultural and health system factors that could be modified both inside the home and in the community in order to prevent child illness and return sick children to health [11]. The Three Delays model, which was originally developed to explore barriers to care–seeking for maternal deaths, had been used to understand access to care and care–seeking practices for newborns [12].

"Social autopsy" instruments based on the Pathway to Survival have been developed to collect the data needed to connect the fatal illness or the act of diagnosing or recognizing that illness to a set of socio–demographic, economic, and cultural conditions or factors, thereby making a social "diagnosis" of the deaths [13].

Implicit in the Pathway to Survival is the continuum of care that has been a recurrent theme in the maternal, newborn and child health literature [14]. The interventions reviewed in the continuum of care and related to the Pathway to Survival framework are classified according to service delivery strategies across the continuum and include key preventative interventions, either inside or outside the home, for which a reasonable level of evidence of efficacy is present and that support the child's wellness [11,15].

The WHO/UNICEF–supported Child Health Epidemiology Reference Group (CHERG) was established in 2001 to provide external technical guidance and global leadership to improve epidemiological estimates of child morbidity and mortality. While most CHERG activities entail gathering and reviewing existing data and building models to develop estimates, verbal/social autopsy (VASA) studies conducted by local partners with CHERG's technical assistance are collecting new data to directly measure causes of neonatal and child mortality and its determinants in several high priority countries. Thus, a study using an integrated verbal and social autopsy questionnaire was conducted to identify the causes and determinants of neonatal (0–27 days) and young children (1–59 months) deaths in Doume, Nguelemendouka and Abong–Mbang districts, Cameroon from 2007–2010.

The current paper focuses solely on the social autopsy component and aims to shed light on social, cultural, or health systems factors that led to newborn's death. To the best of our knowledge, there is no prior study of the social autopsy of neonatal deaths in Cameroon. The process of connecting the diagnosis of a fatal illness to a set of social, cultural, or health systems conditions or factors that contributed to the illness has been described previously as the social diagnosis approach [16]. This integrated perspective potentially provides a broader context for social researchers, programs and policy makers to identify modifiable factors that can be addressed or reinforced to improve the design and implementation of maternal, neonatal and child health programs in Cameroon.

METHODS

Study sites/districts and sample

The VASA interviews in Cameroon were conducted on deaths identified by a census of 16 954 households undertaken by Population Services International (PSI) from October to December 2010 for the Department of Foreign Affairs, Trade and Development of Canada (DFATD) – funded

Home–Based Management of Malaria project in Doume, Nguelemendouka and Abong–Mbang districts. These districts border one another and are located in the East Region of Cameroon. Child mortality in the East region is the second highest in the country at 187 deaths/1000 live births. The survey identified all deaths of children in the prior 10 years from a full birth history of all women age 15–49 years.

To limit issues related to faulty recall, while obtaining an adequate sample size, the VASA study examined deaths of children up to 59 months of age with a 4–year recall period. There were 330 neonatal (0–27 days) deaths and 930 young child (1–59–month old) deaths from 2007 to 2010. Assuming 10% loss due to household relocation and refusals to participate, sample sizes of 330 neonatal deaths and 660 young child deaths (total: 990 deaths) were selected to achieve precision of ±0.05 around the point estimate for the most common cause of young child deaths, and ±0.07 for neonatal deaths, based on an assumed proportion of 50%. Starting with the most recent under–five years old death (whether it was a neonate or child) in all the households and moving back in time, we selected the one most recent under–five years old death (or one at random if there were two or more most recent deaths in the same month) in each household with at least one such death until we had achieved our desired sample sizes in each age group, ie, 330 neonatal deaths and 660 young child deaths. This sampling strategy was previously compared with another one that selected one death at random from each household in the same time period and there were no substantial differences in the child's age at death or sex or in the respondent's age. Thus, we retain the approach of selecting the most recent deaths in order to limit the recall period as much as possible, while maintaining the representativeness for each age group within the time period covered by the deaths in that group.

Data collection tools and VASA interview

The VASA questionnaire blends the Population Health Metrics Research Consortium (PHMRC) verbal autopsy questionnaire to determine the biomedical cause of death, with the CHERG Pathway Analysis social autopsy (SA) questionnaire [17] to inquire about well–child and illness events leading up to a death. The CHERG SA questionnaire updates an earlier Pathway Analysis instrument [18] in order to more fully examine the household, community and health system determinants of neonatal and child mortality, including maternal preventive and curative care in the event of a neonatal death or stillbirth. Unlike the full birth history module used by the PSI census, the VASA allows to further investigate any deaths by asking the respondent if the baby moved, breathed, and cried at birth. When the answer was "No" to all of these items, the software assigned this case to the stillbirth category.

All the illness preventive and curative factors included in the SA questionnaire (**Table 1**) were derived from evidence–based interventions contained in the Lives Saved Tools [19], were judged by a Cochrane review to have good evidence of efficacy, or are among the newborn interventions recommended by the WHO. In addition, where possible, the questions were worded similarly to those in the Demographic and Health Surveys (DHS) [20] in order to allow comparisons of the social autopsy data with similar

Table 1. CHERG Social autopsy questionnaire content

Family (cultural) factors:
Mother's age, education, literacy, marital status, age at marriage
Household possessions (VA), husband's education, breadwinner's occupation
Pre–pregnancy conditions, ANC provider(s), times & timing of last visit
Knowledge/recognition of and care–seeking for pregnancy, labor and delivery complications
Delivery place, decision maker and factors constraining institutional delivery
Home delivery and newborn care (SBA, delivery surface, cord care, bathing, warmth, breastfeeding)
Infant/child care (smoke exposure, ITN, breastfeeding and nutrition, bottle feeding, pre–illness conditions)
Newborn/infant/child illness recognition, health care–seeking, compliance with treatment & referral advice
Constraints to maternal and child health care–seeking, and constraints to compliance with referral advice for maternal complications and treatment and referral advice for newborn and child illnesses
Community (social) factors:
Residence place, duration of continuous residence, and time to reach usual health provider
Social capital (community joint action, helpful persons/groups, denial of services)
Health systems factors:
ANC content (BP, urine & blood, counseling on food & care–seeking), TT, ITN, malaria prophylaxis
Delivery care (attendant, partograph use, hygiene, delivery surface)
Newborn care (resuscitation, cord care, bathing, warmth, post–partum counseling, well–baby checks)
Infant/child care (vaccinations, vitamin A)
Quality of maternal and child health care and delivery of services (treatment, referral & reasons for referral for maternal complications and sick children)

CHERG – Child Health Epidemiology Reference Group, VA – Verbal autopsy, ANC – antenatal care, SBA – community-based agents, ITN – insecticide treated nets, BP – blood pressure, TT – tetanus toxoid

data for survivors in settings where a recent DHS was conducted.

The verbal and social autopsy questions are chronologically blended, with social autopsy questions on preventive care asked first, then the verbal autopsy to identify the signs and symptoms of the illness that led to death, followed by social autopsy questions to assess the perception of the illness and care seeking carried out by the caregiver of the deceased person. The VASA questionnaire was developed in English and, for the study in Cameroon, was translated to French, which is understood by the majority of persons in the study area. Local languages, including Mongo–Ewondo and Maka, which are spoken by a large majority but not all local ethnic groups, as well as Baka, Mpoong moon, Onveng and Abakoum also were used. It would be cumbersome to conduct an entire interview in these languages, which are not written. Therefore, only the local terms for key questionnaire items, such as illness signs and symptoms and the names of local traditional and formal health care providers, were translated to the local languages. The first version of this translation was back–translated into French by a separate team of translators. Any discrepancies were reconciled by the translators before the translations of the final list of key terms were validated, phonetically transliterated and inserted into the French questionnaire. Finally, the translations were inserted into a CSPro software application that was developed to enable direct, field–based Computer Aided Personal Interview (CAPI) capture of the VASA interview data on a netbook computer. The CAPI capture allows for automated implementation of skip patterns and internal consistency checks that considerably improve the quality of the interview being conducted.

For the field work, twenty female interviewers who were native speakers of the local languages and had at least a high school education, received 10 days of in–classroom training in the VASA study background, procedures, ethical standards and conduct of the interview on the netbook, followed by 3 days of field practice, all conducted in French and the local languages. The interviewers were split into three groups (one per district) based on their knowledge on the districs, the local languages and their prior involvement during the mortality survey conducted by PSI in 2010. Each team was led by one field supervisor from the National Institute of Statistics of Cameroon and in addition received two field visits by office supervisors during the forty data collection days. The interviewers were trained to select as the respondent the person most knowledgeable of the child's fatal illness and care provided to the child for the illness. The interview covered the fatal illness from onset to death, including for neonatal deaths, the mother's pregnancy and delivery. Hence, additional eligible respondents were permitted if necessary. In cases with discordant responses among respondents, the main respondent's answers outweighed that of the others.

Most of the fieldwork was conducted from 1 April to 15 May, 2012. Review of the collected data revealed 149 cases with large discrepancies between the expected (from the PSI survey) and observed birth dates, ages at death and/or gender of the deceased children. In addition, 71 households were missed (after three attempts of interview) during the first round of data collection for several reasons, such as the family having temporarily or permanently moved outside of the study area or no eligible respondent having been available at the time of the visit. Thus, revisits of these cases were conducted in August 2012 either to ascertain that the VASA interview was conducted for the correct child, to confirm the child's birth date, age at death and gender, and to re–interview cases as needed, or to attempt to locate the missing family and conduct the interview. Through the revisits, all of the discrepant cases were resolved and only 3 of the 71 first missed interviews were completed with the eligible respondents being present at the time of revisits.

Data analysis

A descriptive analysis was conducted of the data on preventive and curative care, guided by the coverage of key indicators along the continuum of normal newborn care for well children and the steps of illness recognition and care seeking for child illnesses in the Pathway to Survival model [17–19]. The study added an extended pathway for neonatal illnesses that examined the continuum of normal antenatal care and recognition of and care–seeking for maternal complications during pregnancy, labor and delivery.

Definitions of the maternal complications are found in the **Online Supplementary Document**.

For the neonates, in addition to examining the coverage of illness recognition, caregiving, care–seeking and quality health care provision at each step along the Pathway to Survival, we assessed the neonates' median age in days at illness onset, defined as the age when the first symptoms of the fatal illness were recognized, the median illness duration in days, defined as the time from illness onset till death, and caregivers' perception of the children's illness severity at onset, when first deciding to seek formal health care, and at discharge from the first formal provider. Median values are reported for the age at illness onset and the illness duration due to the skewed values for these two variables.

A scoring system was developed to rank caregivers' perception of their children's illness severity. Perceived severity was ranked 1 (normal/mild), 2 (moderate) or 3 (severe) based on combining the scores for the child's reported feeding behavior (normally, poorly or not at all), activity level

(normal, less active or not moving) and mental status (alert, drowsy or unconscious). For each of these three parameters, a score of 0, 1 or 2.5 was assigned according to the child's placement along the respective continuum; the individual parameter scores were then combined, with total scores of 0–2, 2.5–3 and 3.5–7.5 being assigned, respectively, to the final ranks of 1, 2 and 3. Feeding behavior, activity level and mental status were used for the scoring system because they reflect children's actual illness severity as well as mothers' perception of illness severity and the need to seek health care [21–23]. A balance between possibly discordant bio-medical and socio–cultural definitions of certain illness signs was sought by ranking reported unconscious mental status in combination with "feeding normally" or "normally active" as indeterminate (or missing data).

In the development of the severity scoring system, Cronbach's alpha coefficients [24] were derived to assess the consistency of responses to the score items. The coefficients of the summated scores showed values of 0.84, 0.86 and 0.87 at onset of illness, at time decision to seek care was made, and after leaving the health provider, respectively. Hence, the items in the scores, ie, feeding behavior, activity level and mental status elicited highly consistent responses, justifying the reliability of the summated scores [25].

Ethical considerations

Ethical clearance for the VASA study was obtained from the Johns Hopkins School of Public Health's Institutional Review Board and the Cameroon National Research Committee. All respondents provided informed consent before the interview was conducted.

RESULTS

The VASA interview was completed for 267 (81%) of the 330 neonatal deaths identified by the PSI survey. Of these, 158 were confirmed as neonatal deaths, while 75 and 34 were identified during fieldwork as, respectively, young child deaths and stillbirths. Six of the initially sampled young child deaths were identified as neonatal deaths. As such, the social autopsy analysis was conducted on 164 neonatal deaths.

Demographic and household characteristics

Table 2 presents the demographic characteristics of the deceased newborns. Half of the newborns got sick and died within the first 24 hours after birth, and about 71% of the deaths occurred within the first week. Fifty–nine percent of newborn deaths were boys and 41% were girls, for a masculinity ratio of 141. The majority of births (56.1%) and deaths (56.7%) occurred at home. Of the 64 neonates

Table 2. General mortality indicators and demographic characteristics of 164 neonatal deaths, Cameroon, 2007–2010

Characteristics	Frequency (No.)	Percent
Median age at death (in days)	1 (mean 4.0; SD = 5.35)	
Age distribution at death:		
0–6	116	70.7
7–27	47	28.7
Don't know	1	0.6
Sex:		
Boy	96	58.5
Girl	68	41.5
Masculinity ratio (Boy/Girl ×100)	141	
Place of birth:		
Hospital	52	31.7
Other health provider or facility	12	7.3
On route to a health provider or facility	2	1.2
Home	92	56.1
Other	6	3.7
Delivery mode:		
Vaginal	296	92.6
Caesarian	22	6.9
Don't know/Missing	2	0.5
Place of death:		
Hospital	50	30.5
Other health provider or facility	5	3.1
On route to a health provider or facility	10	6.1
Home	93	56.7
Other	6	3.6
Born and died at the health facility (without leaving the facility, n = 64)	40	62.5
Median age at illness onset (in days)	1 (mean = 3.0; SD = 4.16)	
Median illness duration (in days)	1 (mean = 2.5; SD = 8.19)	

SD – standard deviation

born at a health facility, 40 (63%) died at that facility, ie, they did not leave the facility alive.

Table 3 shows the characteristics of the mother, her domestic partner and the household. Eight in ten (76.2%) mothers of the deceased children were married or were cohabiting with a man at the time of their newborn death. Marriage occurred early for these mothers, with the vast majority (74%) entering into a union before their 20th year. In most of the cases (65%), the breadwinners of the households were farmers or agricultural workers. In this study, only 26% of households had electricity, 21% used in–house piped water supply and 18% used improved sanitation, such as a flush or improved pit toilet. The risk of indoor pollution from cooking fuel was present because 32% of households cooked in the house, 93% used firewood for cooking, and there were on average 6 individuals in the household. It took on average 39 minutes for the caregiver to reach the nearest health center from his/her household. The family had been living in the same community for more than 12 years, yet 48% of mothers did not have anyone to help them during pregnancy or a child illness.

Table 3. Characteristics of the mother and her household, 164 neonatal deaths, Cameroon, 2007–2010

| MATERNAL CHARACTERISTICS	FREQUENCY (No.)	PERCENT
Married or living with a man	125	76.2
Mean age when first married (years):	18.0 (median 17, range 12–33)	
<16	34	27.2
16–19	58	46.4
20+	33	26.4
Mother's mean age at time of child death (in years):	22.7 (median 21, range 11–45)	
<16	25	15.2
16–19	42	25.6
20–24	39	23.8
25+	53	32.3
Don't know	5	3.0
Mother's mean years of maternal schooling:	5.9 (median 6, range: 0–22)	
0–3	20	12.2
4–6	92	56.1
>6	52	31.7
Father's mean years of schooling:	7.1 (median 6, range: 0–13)	
0–3	4	3.9
4–6	50	48.5
>6	49	47.6
Household characteristics		
Main breadwinner:		
Father	114	69.5
Mother	12	7.3
Other	38	23.2
Main breadwinner's is farmer/agricultural worker	107	65.2
Household size (Mean)	7.0 (median 6, range: 1–24)	
Household has electricity	42	25.6
Use of piped water, –in–house water supply	35	21.3
Use of improved sanitation (flush or improved pit toilet)	30	18.3
Separate room for cooking	112	68.3
Household uses firewood for cooking	152	92.7
Floor of the house made of cement	32	19.5
Mean travel time to usual health facility (min)	41 (median 30, range: 0–270)	
Average time at current residence	12.2 (median 9, range: 0–55)	
Social capital		
In last 3 years, community worked together on at least 1 of the following: schools, health, jobs, credit, roads, public transport, water, sanitation, agriculture, justice, security, mosque/church	156	95.1
Mother and her family have never been denied any of the following community	104	63.4
Mother was NOT able to turn to any persons or community groups or organizations for help during the pregnancy or child's fatal illness	85	51.9

Maternal and newborn care

Figure 1 presents maternal complications and care–seeking during the pregnancy and/or delivery. During their pregnancy (before labor), 24%, 15% and 11% of the mothers suffered from anemia, sepsis and antepartum hemorrhage, respectively. The main labor/delivery complications that started at home comprised intra–partum hemorrhage (29%), preterm delivery (26%), and prolonged labor (15%). Overall, just half of the mothers (37 out of 72 or 52%) with a pregnancy complication sought some formal care. Less than a quarter (24%) of the 90 mothers with at least one labor and delivery complication that began at home sought some formal care.

Among the 64 neonates born at a health facility, 50% of the mothers of 40 newborns who did not leave alive had at least one labor/delivery complication that started at home, compared to 46% (with at least one labor and delivery complication that started at home) of the 24 who left alive, and the difference was not statistically significant. Among the 40 mothers whom babies were born and died a health facility (without leaving alive) 12 (30%) suffered from anemia during pregnancy; and during labor or delivery, 17 (42.5%) and 11 (27.5%), reported on intra–partum hemorrhage and preterm–delivery complications, respectively.

Figure 2 shows the components of the antenatal care among mothers who completed at least one visit. During the preg-
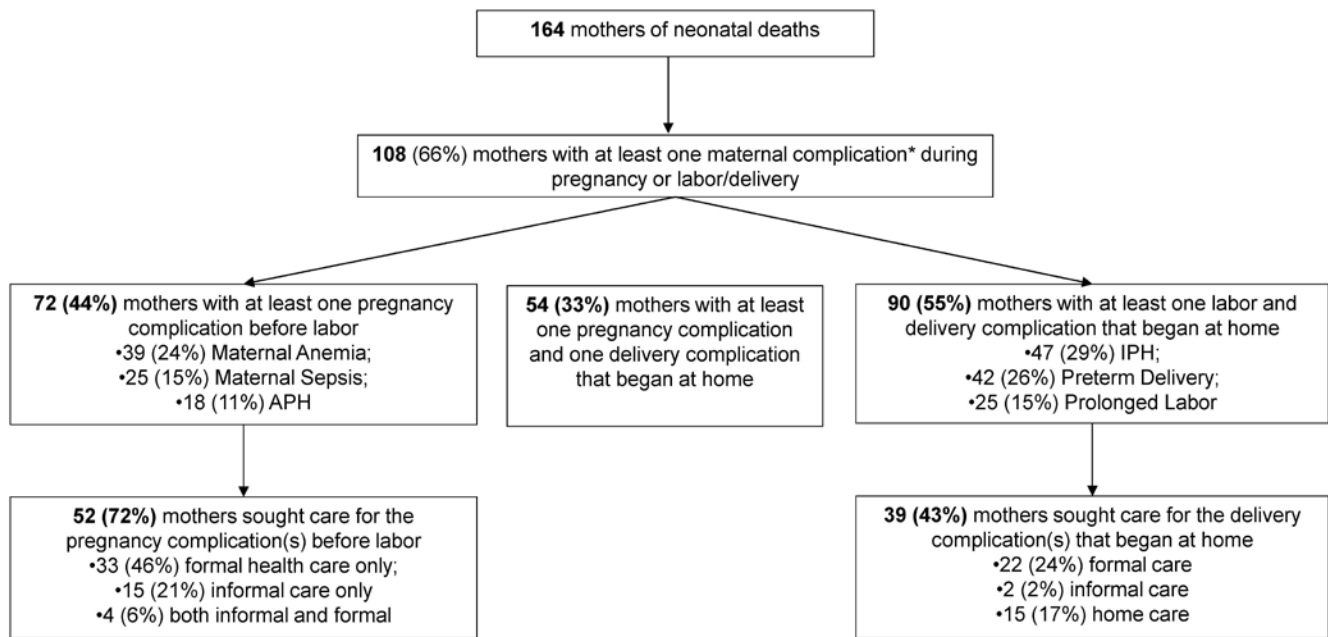
Figure 1. Maternal complications syndromes and care-seeking during the pregnancy and delivery (N = 164). *Maternal complications: Antepartum hemorrhage (APH) – Any vaginal bleeding before labor; Preeclampsia/eclampsia – Puffy face and [blurred vision or severe headache or high blood pressure] and /or Convulsions and no fever and no history of convulsions; Maternal sepsis – Fever and (severe abdominal pain or smelly vaginal discharge or foul smelling liquor); Maternal anemia – (Severe anemia or pallor and shortness of breath) and (too weak to get out of bed or fast or difficult breathing); Intrapartum hemorrhage (IPH) – Excessive bleeding during labor or delivery; Preterm delivery – Less than 9 months; Prolonged labor – Labor for 12 hours or more.
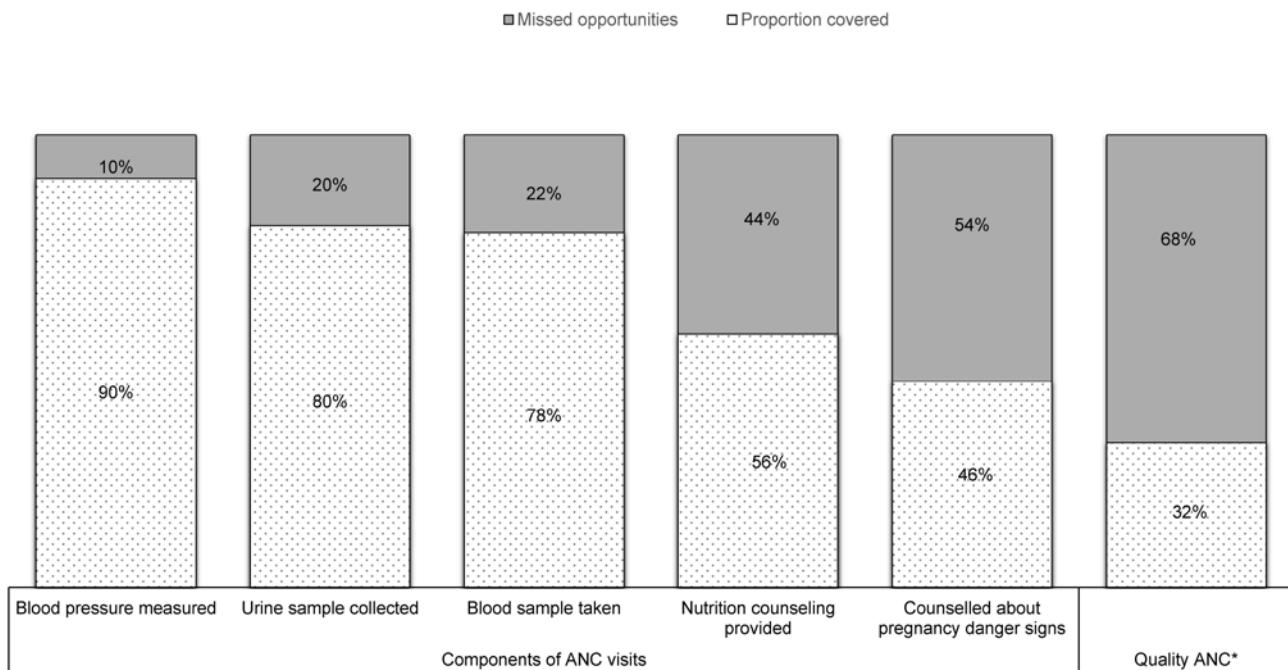
Figure 2. Quality gap for at least one antenatal care visit (N = 125). For women who went to at least one antenatal care (ANC) visit (N = 125), a quality gap (or missed opportunity) exists and represents the difference between the expected maximum coverage and the actual coverage proportion. *Quality ANC includes blood pressure checked, urine and blood tested, nutrition counsels, and counsels about danger signs.

nancy of the deceased neonates, 39 (24%) of the mothers did not benefit from any antenatal care (ANC). For women who went to at least one ANC visit, a quality gap exists because some of them did not receive all of the ANC components, including blood pressure measurement, urine and blood sample tests, and counseling on proper nutrition and pregnancy danger signs. Thus, ANC of "quality" suggests all of the ANC components were provided, ie, blood pressure checked, urine and blood tested, nutrition counsels, and counsels about danger signs. Hence, of the 125 mothers who went to a health provider for at least one ANC visit, only 32% of the mothers received ANC of "quality". And the quality gap or missed opportunity ranged from 10% for blood pressure checked to 54% for counselling about danger signs.

Figure 3 shows the preventive care received by mothers and newborns along the continuum of care. Just 37% of the mothers benefited from the recommended four or more ANC visits. Forty percent of mothers of deceased neonates delivered at a health facility. Overall, 43% of the 164 mothers were assisted by skilled birth attendants, ie, doctors, nurses or midwives. Among those who survived the first day of life, about 49% received appropriate thermal care consisting of immediate warming, drying and wiping, wrapping in a blanket, skin to skin contact with the mother or being placed in an incubator, plus bathing delayed for more than 24 hours after birth. Overall, 33.5% of the mothers breastfed their newborns in the first 24 hours after birth (result not shown). Yet, early initiation of breast-

feeding, ie, within one hour after birth, was lower at 6%. And 23% were provided hygienic cord care. Hygienic cord care suggests a new boiled razor blade from the delivery kit was used for cutting the cord, a clean boiled piece of thread from the delivery kit was used for tying the cord and nothing was applied to the umbilical cord stump after birth or in case something was applied, either alcohol or other antiseptic or antibiotic ointment in cream or powder form was applied.

Figure 4 shows the study findings based on the Pathway to Survival model for 123 newborns with an opportunity for careseeking, including those who were born at home or were born in a health facility and left the facility alive. Forty (24%) of the 164 neonates included in the study sample died at the facility where they were delivered, and one was born at home but was missing all information of careseeking.

At the onset of the 123 newborns' fatal illnesses, 98% of caregivers could recognize and report a severe or possibly severe symptom. Yet, only 55 (44.7%) caregivers provided home care or sought or tried to seek outside care for their newborn child. Twenty–one (17.1%) newborns "died immediately" and no care was given or sought for another 47 (38.2%). Most (70–75%) of the neonates in these last two groups were ranked as being severely ill at the onset of their illness, compared to 44% of those for whom any care was given or sought. Understandably, in the group of those who died "immediately", the age at illness onset and duration were both 0–day, meaning the newborns were born and died quickly
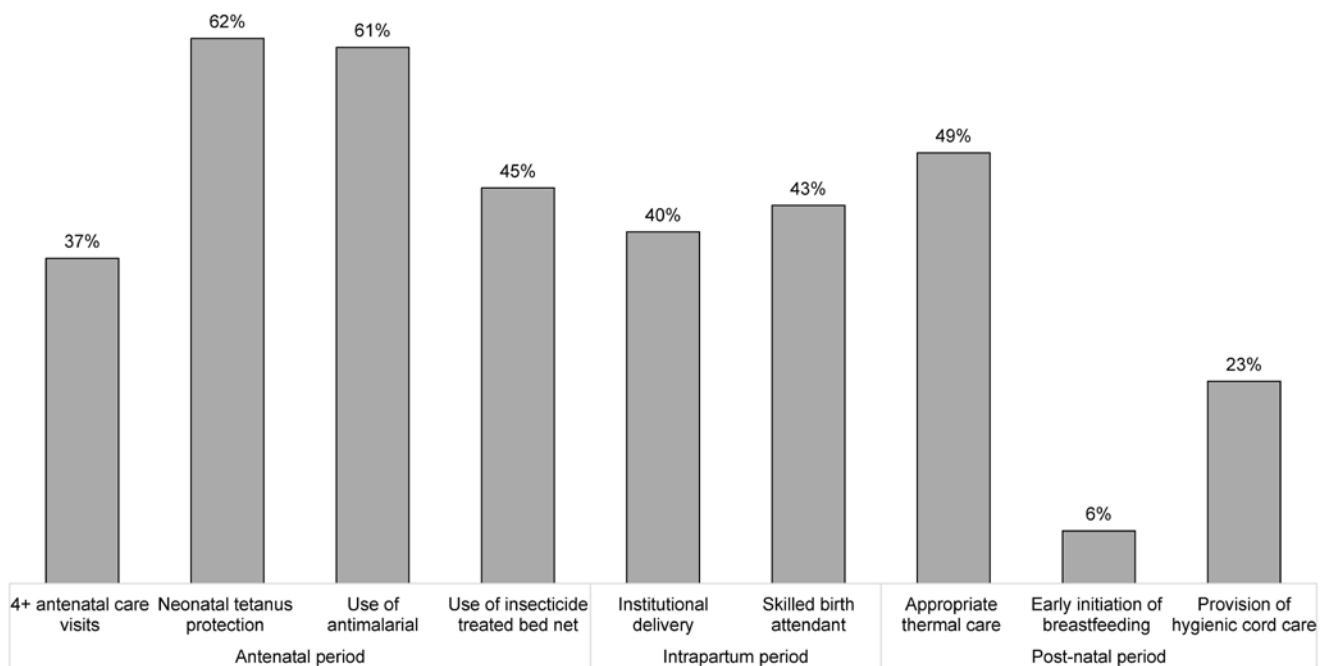
Figure 3. Preventive care of the mothers and newborns (N = 164).
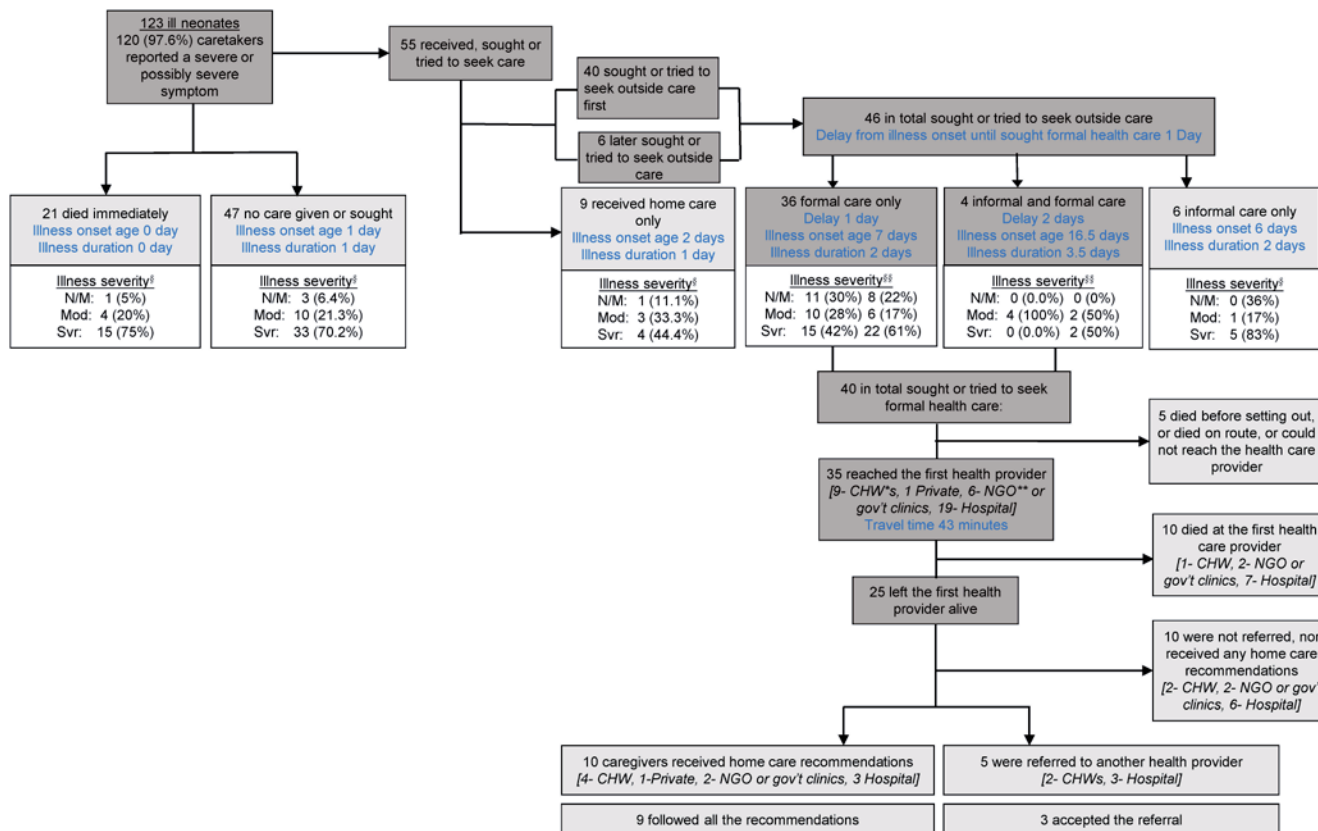
Figure 4. The "Pathway to Survival" for 123 neonatal deaths (born at home or left the delivery facility alive). §Illness severity at onset; §§Illness severity at onset and when caregiver decided to seek formal care; N/M – normal/mild, Mod – moderate, Svr – severe; *CHW – Community Health Worker, **NGO – Non-governmental organization.

(or "immediately") the same day of birth. Conversely, for newborns in the group that received no care, the illness occurred on the second day of life and lasted just 1 day.

Of the 55 neonates who received, sought or tried to seek care, 40 first sought care outside the home, 15 first received care inside the home, and 6 of these 15 later sought or tried to seek outside care. Among the 46 who sought any outside care, 36 sought formal care only, 4 sought both informal and formal care, and 6 sought informal care only. The median delay from the onset of illness until formal health care seeking was 1 day. The delay to seeking formal care when both informal and formal care were sought (2 days) was greater ($P<0.05$) than the delay when formal care only was sought (1 day).

Of the 40 newborns for whom formal care was sought, more than half were already severely ill at the time the caregiver decided to seek care. Five neonates did not reach the health facility because they died either before setting out or on route or could not reach the health provider. The remaining 35 newborns reached the first health provider after on average 43 minutes travel time. Nine went to a community health worker (CHW), 1 to a private doctor or clinic, 6 to a non-

governmental- organization (NGO) or government clinic, and 19 to an NGO or government hospital.

More than one–third (37%, n = 7) that went to an NGO or government hospital died without leaving that hospital. Another child died at the CHW and 2 others at an NGO or government clinic. Of the 25 who left the provider alive, 10 received home care recommendations, 5 were referred to another health care provider, and 10 were sent home without being referred or given any home care recommendations.

It is worth mentioning that of the 8 newborns who went and left a CHW alive, just 2 were referred to a second provider. Yet, 4 of the 6 caregivers who were not referred reported that their newborns were severely ill at discharge from the CHWs.

Figure 4 also shows that when recommendations were received, most caregivers (9 out of 10) followed them all. Similarly, when the 5 neonates were referred, 3 of them accepted the referral and went to a second health provider.

Figure 5 explores the care–seeking constraints for the delivery and for the neonatal illness. Of the 99 mothers that
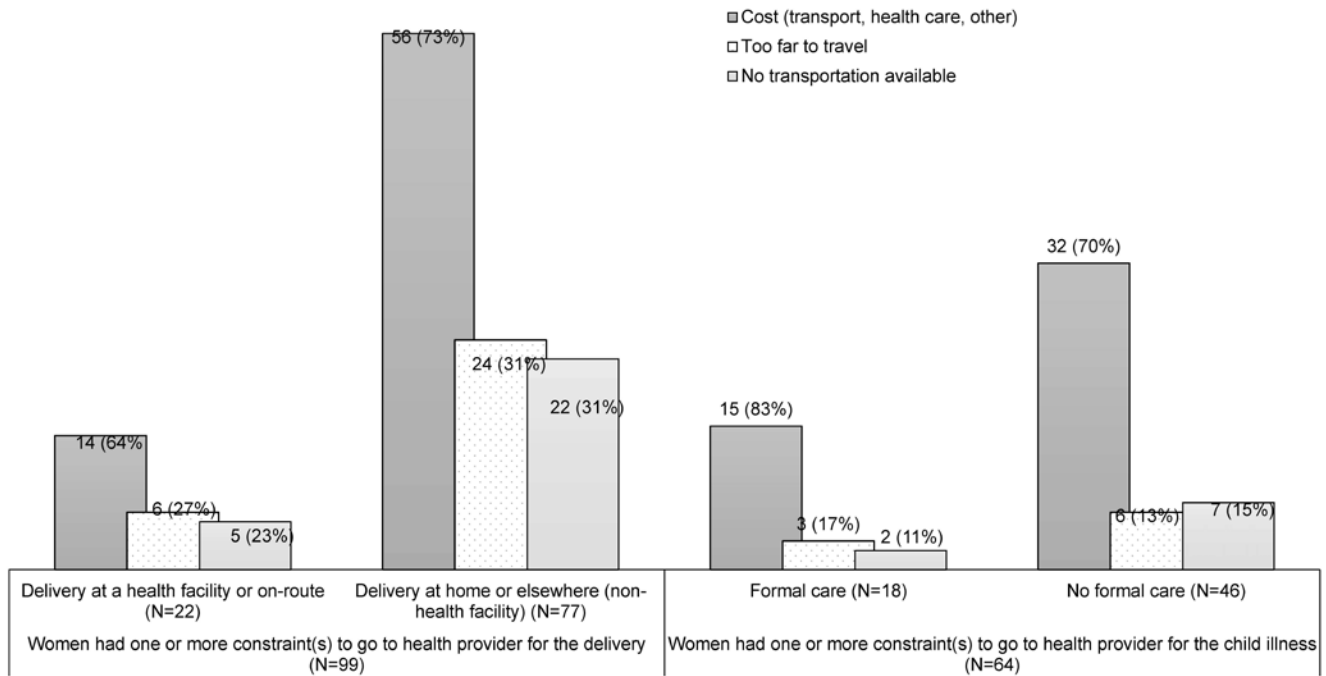
Figure 5. Main care–seeking constraints for the delivery and for the neonatal illness.

reported concerns or problems for delivering at a health facility, the majority (77.8%, n = 77) delivered at home or another place other than a health facility. Similarly, of the 64 caregivers that mentioned one or more constraints for seeking formal care for their newborn's illness, the majority (71.9%, n = 46) sought informal care only or did not seek any care at all. Among the problems reported both during delivery and during the newborn fatal illness, the cost for transport and/or health care, distance to reach the provider and lack of transportation emerged as the most important constraints.

DISCUSSION

The objective of this study was to explore the household, community and health system determinants of neonatal mortality in Doume, Nguelemendouka and Abong–Mbang health districts, in Eastern Region of Cameroon from 2007–2010.

Demographic and household characteristics

Our study findings showed that the vast majority of the deceased newborns lived in poor households lacking basic commodities such as electricity, improved sanitation and clean water. The households were crowded and more than nine–tenths used firewood for cooking. Most families' breadwinners were farmers. These impoverished conditions of households in this study could have contributed

to the neonatal deaths. Indeed, previous studies have highlighted an increased risk of neonatal deaths of poor families because they face more challenges in accessing timely, high quality health care compared to wealthier families [26,27].

Differences in mortality rates for male and female children are highest during the neonatal period. Baby girls have a lower mortality rate than boys in societies where equal care is offered to both sexes [28].Similarly in the three study districts, the number of newborn deaths was 1.4 times higher among male than female children.

The majority of the deceased newborns were born to young mothers less than 20 years of age. Elsewhere, complications of pregnancy and childbirth have been described as the leading causes of perinatal death of babies born to mothers under 20 years of age, as adolescent mothers' babies are more likely to be of low birth weight and/or to be born prematurely [29]. Understandably, WHO has developed extensive guidelines to prevent early pregnancy and its poor health outcomes by preventing marriage of adolescents, by increasing knowledge and understanding of the importance of pregnancy prevention, by increasing the use of contraception and by preventing coerced sex [30].

Maternal complications and care during pregnancy, labor and delivery, and immediate post–neonatal care

Huda et al. estimated that complications during labor and delivery increased the risk of perinatal mortality deaths [31]. Globally, complications from preterm births, intra-

partum–related disorders or birth asphyxia, and infections have been consistently reported as the leading causes of neonatal deaths [32,33]. In the current study, labor and delivery complications that started at home occurred in more than half of the pregnant mothers of the deceased newborn. Yet, very few sought formal care when those complications occurred, thereby adding to the increased risk of deaths of their newborns. Therefore, early recognition, immediate care–seeking and referral (when necessary) of women with obstetric complications should be a program priority. Equally, basic and comprehensive emergency obstetric care that includes essential and emergency newborn care and newborn resuscitation is marked by a series of core competencies defined by the World Health Organization (WHO), the International Council of Midwives (ICM), and the International Federation of Gynecology and Obstetrics (FIGO) [34].

This study also revealed that one in five mothers of the deceased newborns did not receive any antenatal care, thereby, significantly increasing the risk of perinatal mortality [29]. ANC is a health service package that links the woman and her family to the health system during pregnancy. Not only does it directly improve the survival and health of babies by reducing stillbirths and neonatal deaths, but it also constitutes an entry point for health facilities contacts with women [35].

In addition, while coverage of at least one antenatal care visit, at 79%, was relatively high in these three districts in Cameroon, coverage of the recommended minimum four–visits, at 37%, was much lower. And even when they had contact with the health system during their pregnancy, more than two–thirds of mothers did not receive high quality antenatal care. Indeed, more than one antenatal visit is required for a health provider to record a mother's medical history, assess her individual needs, conduct screening tests, provide advice and guidance on pregnancy and delivery educate on self–care during pregnancy, identify conditions detrimental to health during pregnancy, provide first–line management, and referral if necessary [36,37]. This quality gap found in our study demonstrates key missed opportunities that could have saved several lives within the health system.

The VASA study also highlighted the low coverage of other key interventions along the continuum of care, such as delivery at health facility, skilled birth attendants, hygienic cord care, appropriate thermal care and early initiation of exclusive breastfeeding. Previously, health facility delivery has been found to reduce the risk of neonatal mortality by 29% in developing countries [38]. And if practiced routinely at both community and facility levels, it is known that hygienic cord care, proper thermal care and early initiation of breastfeeding practices, could reduce newborn deaths by up to 30% [39].

Newborn care during fatal illness

At the time caregivers first noticed the illness, 65% of neonates were severely ill, meaning they could not eat at all, they were unconscious/or and they could not move. Timing is critical to providing neonates with appropriate care at the onset of illness, and delays in deciding to seek care can have significant consequences [33]. While the first, fundamental, step in taking this decision is for caregivers to be able to recognize illness danger signs, this can be particularly challenging in the neonate due to the lack of specific symptoms [40–42]. In addition, careseeking was delayed for several neonates who became sick after the first week of life and whose illnesses were less serious at the onset until they became more severely ill. Other studies have described interventions to promote maternal recognition of neonatal illnesses and careseeking before the child becomes severely ill [43,44].

In Cameroon, the community–based Integrated Management of Childhood Illness (C–IMCI) strategy was also designed to focus on the major causes of death in children under–five through improving case management skills of health workers, strengthening the health system, and addressing family and community practices. However, C–IMCI modules, like in other developing countries, did not originally include care of the sick newborn. Hence, the fact that two–thirds of the newborns that went to a CHW were severely ill, yet left without being referred, echoes the need to scale up newborn health interventions using the IMCI strategy. Indeed, current international opinion suggests that incorporating newborn algorithms in IMCI and strengthening the components of the strategy related to the health system and community will directly impact newborn health [45].

Barriers to maternal and newborn care

Barriers to care extend beyond the health service and include issues such as distance, beliefs, financial and transport constraints. The findings show that unaffordable costs for transportation and health care were key barriers to seeking health care, both for pregnancy and labor/delivery complications and for newborn fatal illnesses. These findings suggest a need to mitigate the costs of care–seeking and lack of means of transport. One possibility is to provide finance, either at the central or at the local level, to cover the costs of transport, and user fees. Conditional cash transfers programs, community insurance schemes, coupons and vouchers, and facility funds for cost reimbursements are possible mechanisms [46–48]. One alternative is to provide subsidized transport services to get newborns to hospital, and another, on a more ambitious scale, is the building, or repairing, of local roads and bridges to help people get to the health facilities.
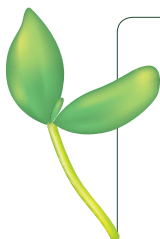
Study limitations

This study had some limitations. Given the recall period of about 4 years, added to the fact that the respondents were the main caregivers of the deceased newborns, it is possible that the data may have been affected by different types of biases, including recall bias of past events and the likelihood of providing socially desirable answers to sensitive questions. However, the conversational and prompting modes used during the face–to–face interviews may have led to better overall recall of events. In addition, the study was conducted in a small area of the Eastern region of Cameroon, rendering it difficult to generalize the findings to the entire country. Given the diversity of cultures and population in Cameroon, a national study could offer a clearer picture of the entire country. Last, the inclusion of a control group would have allowed the analysis to test whether or not there were significant differences between the coverage of interventions among cases (deceased newborns) and controls (alive newborns). However, the lack of a comparison group in social autopsy studies is common and not so necessary since we are studying proven interventions that should be accessible to all pregnant mothers and newborns.

CONCLUSION

The social autopsy study provided a unique opportunity to review the coverage of essential interventions for deceased newborns and their mothers along the continuum of care, to identify the breakdowns within the Pathway to Survival that led to the newborn deaths and to examine the care–seeking barriers during delivery and the newborns' fatal illnesses that contributed to the deaths. Newborns are vulnerable and dependent upon their families for survival, but poor families, especially those in rural, peri–urban and remote areas, such as in Doume, Nguelemendouka and Abong–Mbang health districts, in Eastern Region of Cameroon, do not have the resources necessary to care for their newborns.

Maternal health and well–being play an important role in newborn survival, pointing to the need to strengthen the continuum of care for maternal, newborn and child health. While most women access the formal health system during pregnancy, the number of visits and quality of care must be increased in order to address the gap between service utilization and need around the time of childbirth and the early postnatal period, during which most newborn deaths occur. Challenges at the facility level must be addressed. Yet, the fact that the majority of births and newborn deaths happen at home in these districts means that successful community partnerships, social mobilization, and health education and behavior change communication is also required to improve knowledge of pregnancy related and newborn or child illness symptoms and careseeking behaviors in order to save lives.

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Deriving causes of child mortality by re–analyzing national verbal autopsy data applying a standardized computer algorithm in Uganda, Rwanda and Ghana

Li Liu[1,2*], Mengying Li[1*],
Stirling Cummings[3], Robert E. Black[2]

[1] Department of Population, Family, and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[2] Institute of International Programs, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[3] MEASURE Evaluation, Carolina Population Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

* Joint first authors.

Background To accelerate progress toward the Millennium Development Goal 4, reliable information on causes of child mortality is critical. With more national verbal autopsy (VA) studies becoming available, how to improve consistency of national VA derived child causes of death should be considered for the purpose of global comparison. We aimed to adapt a standardized computer algorithm to re–analyze national child VA studies conducted in Uganda, Rwanda and Ghana recently, and compare our results with those derived from physician review to explore issues surrounding the application of the standardized algorithm in place of physician review.

Methods and Findings We adapted the standardized computer algorithm considering the disease profile in Uganda, Rwanda and Ghana. We then derived cause–specific mortality fractions applying the adapted algorithm and compared the results with those ascertained by physician review by examining the individual– and population–level agreement. Our results showed that the leading causes of child mortality in Uganda, Rwanda and Ghana were pneumonia (16.5–21.1%) and malaria (16.8–25.6%) among children below five years and intrapartum–related complications (6.4–10.7%) and preterm birth complications (4.5–6.3%) among neonates. The individual level agreement was poor to substantial across causes (kappa statistics: –0.03 to 0.83), with moderate to substantial agreement observed for injury, congenital malformation, preterm birth complications, malaria and measles. At the population level, despite fairly different cause–specific mortality fractions, the ranking of the leading causes was largely similar.

Conclusions The standardized computer algorithm produced internally consistent distribution of causes of child mortality. The results were also qualitatively comparable to those based on physician review from the perspective of public health policy. The standardized computer algorithm has the advantage of requiring minimal resources from the health care system and represents a promising way to re–analyze national or sub-national VA studies in place of physician review for the purpose of global comparison.

Correspondence to:
Li Liu
Department of Population, Family, and Reproductive Health
Johns Hopkins Bloomberg School of Public Health
615 N Wolfe Street
Baltimore, MD 21205, USA
lliu26@jhu.edu

To accelerate progress toward the Millennium Development Goal 4 (MDG 4) [1] in 2015 by reducing under–five mortality rate by two–thirds since 1990 and end preventable child deaths in a generation [2,3], reliable and updated information on causes of child mortality is critical for prioritizing

child health interventions and allocating scarce public health resources. For most low– and middle–income countries (LMICs), distribution of child causes of death is usually derived from community–based verbal autopsy (VA) studies applying systematic modeling [4–6]. In the meantime, an increasing number of national VA studies have been conducted and more are becoming available [6–15]. While empirical data mounts to fill the large information gap of causes of child mortality across LMIC [4,6,16], how to improve consistency and comparability of national VA results should be considered for the purpose of global comparison.

VA studies by design should be consistent and comparable when used to generate population level cause–of–death estimates [17]. In practice, the data collection procedures have been relatively standardized in the national VA studies conducted in the past two decades [7,9–15]. However, when applying national VA data to derive cause–of–death estimates, at least two different methodologies have been applied, including physician review, computer algorithm and probabilistic approaches [17]. The methodological differences in these ascertaining approaches impede direct comparison across estimates.

Compared to computer algorithm, physician review has the apparent disadvantage of involving a large team of physicians. This may intervene with the routine function of the health care systems in many LMICs. In addition, physician review derived cause–of–death estimates may have limited internal consistency due to concerns over repeatability of the approach [7,14,15,17]. Physicians may also interpret VA with subjectivity and judgment [17]. Relying extensively on the open narrative of the circumstances surrounding the death event, physicians can use specific diagnostic techniques differing considerably between individuals and settings. Biased by their prior knowledge of local epidemiology, physicians are also found to be reluctant to assign unexpected causes of death, while favoring some highly specific diagnosis without adequate evidence. Even though two physicians can have high level of agreement, the agreement may simply reflect their similar medical experiences, but does not ensure the results are comparable with those generated in a different time or place [17]. Computer algorithm, in contrast, is considered to be capable of producing more comparable results [17–19].

In this study, we aim to adapt a previously developed standardized computer algorithm [8] to re–analyze national child VA studies conducted recently in Uganda, Rwanda and Ghana to improve the comparability of child cause–of–death information across countries. We also aim to compare our results with those originally derived from physician review to explore issues related with the application of the standardized computer algorithm in place of physician review.

METHODS

Ethics statement

The study data were publically accessible and analyzed anonymously. Hence no informed consent was needed.

National VA studies and the inclusion criteria for re–analysis

The three national Child VA studies re–analyzed includes the 2007 Uganda study, 2008 Rwanda study, and 2008 Ghana study [7,14,15]. The three studies interviewed households with eligible child deaths (plus stillbirths in Uganda) identified through birth history collected in the accompanying Demographic and Health Surveys (DHS) [20–22]. A total of 724, 462 and 226 eligible deaths were identified, among whom 641 (86.4%), 431 (93.3%) and 199 (88.1%) interviews were completed in Uganda, Rwanda and Ghana, respectively. The VA interviews were conducted either following the corresponding DHS, or concurrently with the DHS. **Table 1** provides additional details of the three national VA studies.

Table 1. Details of the three national child verbal autopsy (VA) studies

|	2007 Uganda Child VA Study	2008 Rwanda Child VA Study	2008 Ghana Child VA Study
Accompanying Demographic and Health Surveys (DHS)	Uganda DHS 2006	Rwanda Interim DHS 2007–08	Ghana DHS 2008
Number of eligible women interviewed in the DHS	8531	7313	4916
VA eligibility	Death of child less than 5 y, or loss of pregnancy of over 6 mo of gestational age, occurring 36 mo preceding the DHS interview	Death of child less than 5 y occurring 36 mo preceding the DHS interview	Death of child less than 5 y occurring after January 2005
No. of VA eligible deaths	724	462	226
No. of completed VA interview	641	431	199
VA completion rate (%)	86.4	93.3	88.1
Interval between VA initiation and DHS completion (month)	5	1	0
Duration of VA interviews	15 March – 7 April, 2007	20 May – 27 June, 2008	8 September – 25 November, 2008
Maximum length of recall (month)	46	42	47

All three VA studies followed the Sample Vital Registration with Verbal Autopsy (SAVVY) protocol [23]. Specifically, the primary caregiver of the deceased child was interviewed about symptoms, signs, and health care received before death with instruments adopted from the standardized WHO VA questionnaires for neonatal and child deaths [24]. Causes of deaths were originally ascertained by two trained physicians independently reviewing both the structured and open–ended narrative sections of the completed VA questionnaires, and coded according to the International Classification of Diseases, 10th revision (ICD–10). If discordant ICD–10 codes were assigned by the two coding physicians, a single cause of death was agreed upon after deliberation.

We did not have access to the open–ended narrative data and focused the current analyses on the structured section of the VA questionnaires. We applied the following criteria to only include children who: 1) were identified as live births; 2) died between ages 0 and 59 months; 3) had complete VA interviews; 4) had sufficient information on age at death; and 5) were administered age–appropriate questionnaire.

Standardized computer algorithm

We adapted a previously developed standardized computer algorithm to assign causes of death [8]. The algorithm was consisted of case definitions and a hierarchical process. The case definitions were combinations of cause–specific signs and symptoms (see **Online Supplementary Document**). Generally, the algorithm only allowed one cause for each death. But deaths due to measles, diarrhea and acute respiratory infection (ARI) can be assigned simultaneously, and then re–distributed into the respective single cause according to their cause–specific mortality fractions (CSMFs) assigned before the re–distribution. Causes were assigned through a hierarchical process in which diagnoses with more specific symptoms were made before those with less specific ones, and cases without any diagnosis at the end were classified as unspecified conditions (**Figure 1**). The algorithm contained two parallel hierarchies to assign deaths of children aged 0–27 days and 1–59 months. More information of the standardized computer algorithm can be found elsewhere [8].

Considering the disease profile in Uganda, Rwanda and Ghana, we incorporated the following modifications to the standardized computer algorithm. We added malaria and AIDS to account for the large burden of the two conditions in these countries [6]. Specifically, we adopted the malaria case definition from the WHO standard VA method for infants and children [25], and placed malaria after meningitis/encephalitis in the hierarchy for children aged 1–59 months (**Figure 1**). We chose not to assign deaths due to
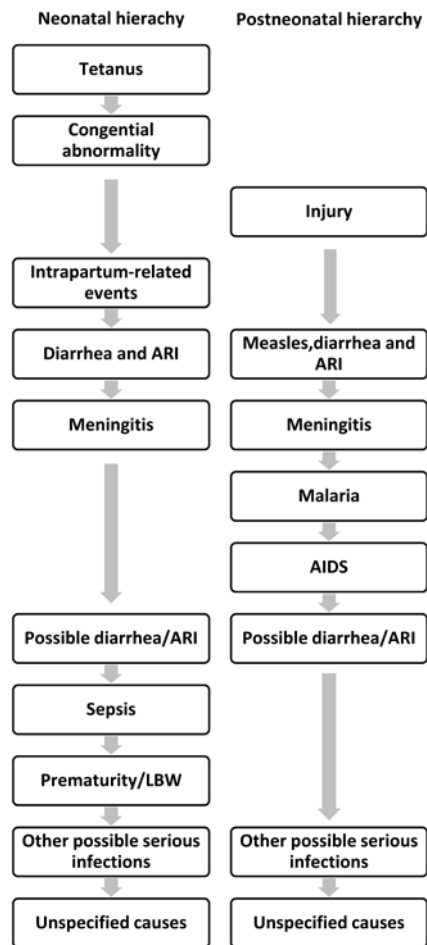
Figure 1. Hierarchy applied in the standardized computer algorithm. This figure provides a visual illustration of the hierarchy used in the algorithm to assign causes of deaths among neonates and children 1–59 months of age.

malaria among neonates due to its low incidence and the associated low accuracy [26].

Due to the lack of information on symptoms of pediatric AIDS cases (eg, oropharyngeal candidiasis, confirmed maternal HIV–1 infection, etc) [27–31], we developed our own preliminary AIDS definition for VA analysis. We first reviewed several pediatric and adult AIDS case validation studies. Then applied major clinical criteria of WHO's pediatric AIDS case definition in combination with selected available common criteria used in a few adult AIDS case definitions with good validity [28,32–34]. Our final AIDS case definition included any of the following conditions: 1) jaundice; 2) chronic diarrhea lasted for more than 1 month; 3) chronic fever lasted for more than 1 month; 4) wasting, defined as having at least 1 of the following symptoms – paleness, hair color change, edema legs, dry scaly skin; and 5) cough or trouble breathing lasting 3 to 27 days with fever but without a recent diagnosis of tubercu-

losis. We chose not to assign AIDS among neonates considering the likely low specificity of our preliminary case definition and the low incidence (only approximately 1.6% of all under–five AIDS deaths occur in the first 28 days (personal communication with Neff Walker). Among children aged 1–59 months, AIDS was placed after malaria in the hierarchy.

We also added meningitis/encephalitis and neonatal sepsis in the algorithm. We adopted case definitions of the two conditions from WHO [25], and placed meningitis and neonatal sepsis after ARI and possible diarrhea/ARI, respectively. Additional minor modifications were made to the case definitions to accommodate variations in signs and symptoms collected across countries. A complete list of standardized case definitions applied in this study in comparison with those used previously [8] is provided in **Online Supplementary Document**.

Cause of death categorization and results comparison

We grouped causes of deaths into categories comparable to the Child Health Epidemiology Reference Group (CHERG) categorization, including among neonates: pneumonia, preterm birth complications, intrapartum–related complications (including birth asphyxia and birth injury) [35], sepsis, tetanus, congenital abnormalities, diarrhea and other neonatal disorders; and among children aged 1–59 months: pneumonia, diarrhea, measles, injury, malaria, AIDS, meningitis, and other infections [6]. The group of remaining non–communicable diseases was not assigned separately due to the lack of sufficient information. **Online Supplementary Document** maps the ICD–10 codes and the cause categories used in the standardized computer algorithm and physician review.

To compare results derived from standardized computer algorithm vs physician review, individual–level concordance within each country was examined using Cohen's kappa, where deaths initially assigned to multiple causes (eg, measles, diarrhea and ARI) were excluded. Population level agreement was also assessed by comparing CSMFs and ranking of the CSMFs of the top five single causes [36]. All analyses were conducted using STATA 11 [37] considering the complex survey design.

RESULTS

Among the 724, 462 and 226 deaths available in the child VA studies in Uganda, Rwanda and Ghana, 530 (126 neonatal and 404 post–neonatal), 360 (121 neonatal and 239 post–neonatal) and 188 (71 neonatal and 117 post–neonatal) deaths met the study inclusion criteria, respectively.

CSMF derived from the standardized computer algorithm

The CSMFs among neonates, children aged 1–59 months and 0–59 months estimated applying the standardized computer algorithm are presented in **Table 2**. Pneumonia and malaria were the leading causes of deaths across all three countries, contributing around one fifth (16.5–25.6%) of under–five deaths. Diarrhea was responsible for more than one–tenth of under–five deaths in Uganda and Rwanda (15.9% and 12.0%, respectively). Major single neonatal causes in the three countries included intrapartum–related complications (6.4–10.7%) and preterm birth complications (4.5–6.3%). AIDS was also an important cause, contributing 3.0–8.6% of total under–five deaths. Roughly 5% of all under–five deaths were assigned to other conditions across the three countries, and the unspecified causes contributed 8.2–25.0% of total under–five deaths.

Agreement between estimates derived from the standardized computer algorithm and physician review

Individual–level concordance between causes assigned by the two approaches is shown in **Table 3**. Only consistent agreement observed in at least two of the three countries

Table 2. Cause specific mortality fractions among children 0–59 mo ascertained by the standardized computer algorithm, Uganda, Rwanda and Ghana

Age group	Uganda (N = 530)	Rwanda (N = 360)	Ghana (N = 188)
Neonates aged 0–27 days			
Pneumonia	2.8	4.4	3.7
Intrapartum–related complications	6.7	10.7	6.4
Preterm birth complications	5.9	4.5	6.3
Congenital abnormalities	1.8	1.9	3.6
Neonatal sepsis	0.4	0.5	0
Other neonatal disorders	2.5	1.5	1.8
Tetanus	2.3	0.9	0.7
Diarrhea	0.2	0.6	0.0
Unspecified	2.1	7.2	13.6
Children aged 1–59 months			
Diarrhea	15.7	11.4	2.5
Malaria	23.2	25.6	16.8
AIDS	3.9	3.0	8.6
Injury	2.8	1.2	3.7
Meningitis	1.8	1.2	1.8
Measles	1.6	0.2	0.5
Other infections	2.0	3.3	3.7
Pneumonia	18.3	12.1	14.9
Unspecified	6.1	9.6	11.4
Total	**100**	**100**	**100**
Children aged 0–59 months			
Pneumonia	21.1	16.5	18.6
Diarrhea	15.9	12.0	2.5
Other conditions	4.5	4.8	5.5
Unspecified	8.2	16.8	25.0

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Table 3. Cohen's kappa (standard error) between results based on computer algorithm and physician review, Uganda, Rwanda and Ghana

Age group	Uganda	Rwanda	Ghana
Neonates aged 0–27 days:			
Congenital abnormalities	0.57 (0.039)	0.22 (0.033)	0.53 (0.073)
Preterm birth complications	0.46 (0.042)	0.31 (0.051)	0.42 (0.065)
Intrapartum–related conditions	0.30 (0.040)	0.51 (0.053)	0.31 (0.071)
Pneumonia	0.19 (0.025)	0.25 (0.050)	0.00 (0.000)*
Tetanus	0.16 (0.038)	0.31 (0.050)	0.32 (0.069)
Sepsis	0.09 (0.018)	0.02 (0.032)	0.00 (0.000)*
Other	0.20 (0.035)	0.04 (0.051)	0.14 (0.037)
Unspecified	0.03 (0.042)	0.00 (0.000)*	0.00 (0.000)*
Diarrhea	0.00 (0.000)*	0.00 (0.050)	–†
Children aged 1–59 months:			
Injury	0.63 (0.043)	0.44 (0.052)	0.83 (0.073)
Malaria	0.46 (0.043)	0.25 (0.051)	0.46 (0.07)
Measles	0.70 (0.043)	0.00 (0.000)*	0.40 (0.058)
Pneumonia	0.26 (0.041)	0.40 (0.053)	0.16 (0.061)
Unspecified	0.27 (0.043)	0.25 (0.053)	0.21 (0.066)
Diarrhea	0.23 (0.038)	0.19 (0.053)	0.28 (0.07)
Other infections	0.14 (0.032)	0.10 (0.050)	0.28 (0.056)
Meningitis	0.10 (0.035)	0.13 (0.047)	–0.02 (0.071)
AIDS	–0.01 (0.043)	–0.03 (0.046)	0.00 (0.000)*

*0 case is assigned in either the physician review or the algorithm.
†0 case is assigned in both the physician review and the algorithm.

are described here in the text. The agreement on injury was at least substantial (kappa ranges 0.61 to 0.80 [38]) in two countries, with the kappa statistics being 0.63 in Uganda and 0.83 in Ghana. The agreement on a number of other causes was at least moderate (kappa ranges 0.41 to 0.60) in two countries, including that on congenital malformation (kappa: 0.57 in Uganda and 0.53 in Ghana) and preterm birth complications (kappa: 0.46 in Uganda and 0.42 in Ghana) among neonates, and malaria (kappa: 0.46 in Uganda and Ghana) and measles (kappa: 0.70 in Uganda and 0.40 in Ghana) among older children. Those causes with fair agreement (kappa ranges 0.21 to 0.40) included intrapartum–related conditions (kappa: 0.30 in Uganda and 0.31 in Ghana) and tetanus (kappa: 0.31 in Rwanda and 0.32 in Ghana) among neonates, and pneumonia (kappa: 0.26 in Uganda and 0.40 in Rwanda), unspecified conditions (kappa: 0.27 in Uganda, 0.25 in Rwanda, and 0.21 in Ghana) and diarrhea (kappa: 0.23 in Uganda and 0.28 in Ghana) among children aged 1–59 months. The rest of the causes all had slight agreement or worse (kappa ranges at or below 0.20) between the two approaches in at least 2 countries.

CSMFs derived from the standardized computer algorithm in comparison with those from physician review among neonates and children aged 1–59 months are presented in

Figure 2 and 3, respectively. The standardized computer algorithm consistently assigned a larger proportion of several causes than physician review among neonates, including pneumonia, preterm births, and congenital abnormalities. Physicians, in contrast, assigned a larger proportion of a few other causes, including neonatal sepsis and other neonatal disorders. Among children aged 1–59 months, no consistent pattern was observed when comparing CSMFs derived from the two methods except that physicians consistently assigned a larger proportion of other infections than the standardized computer algorithm. The discrepancies of malaria–specific mortality fractions derived from the two approaches were huge, ranging between 11 and 23 percentage points, with physicians assigning a higher proportion in Uganda and Ghana and the opposite being true in Rwanda.
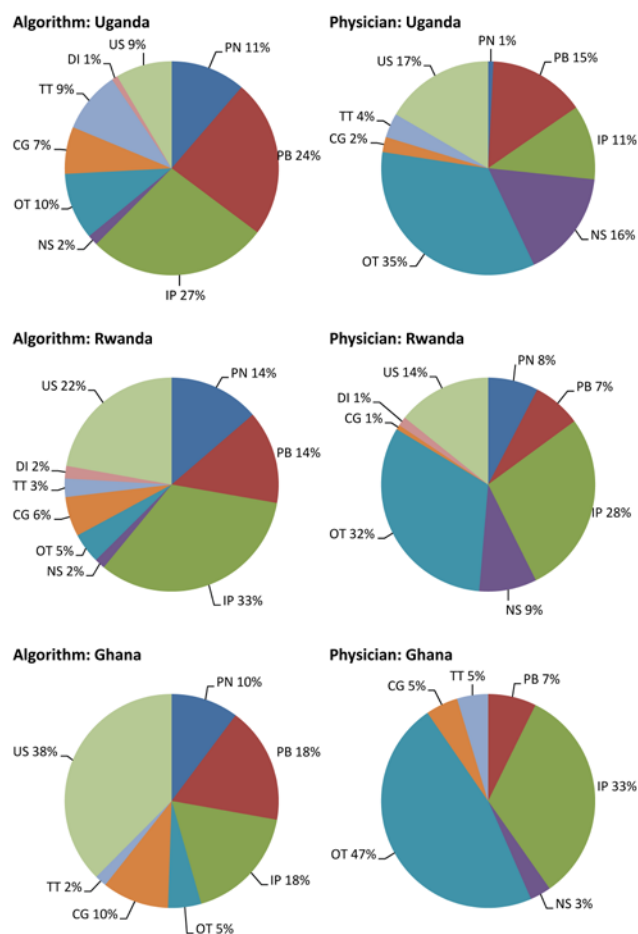
Figure 2. Neonatal cause specific mortality fractions by standardized computer algorithm and physician review, Uganda, Rwanda and Ghana. This figure includes side–by–side pie graphs to compare the cause specific mortality fractions of neonatal deaths generated by standardized computer algorithm and physician review in the three countries. PN – pneumonia; PB – preterm birth/low birth weight; IP – intrapartum–related complications; NS – neonatal sepsis; OT – other neonatal disorders; CG – congenital abnormalities; TT – tetanus; DI – diarrhea; US – unspecified causes.
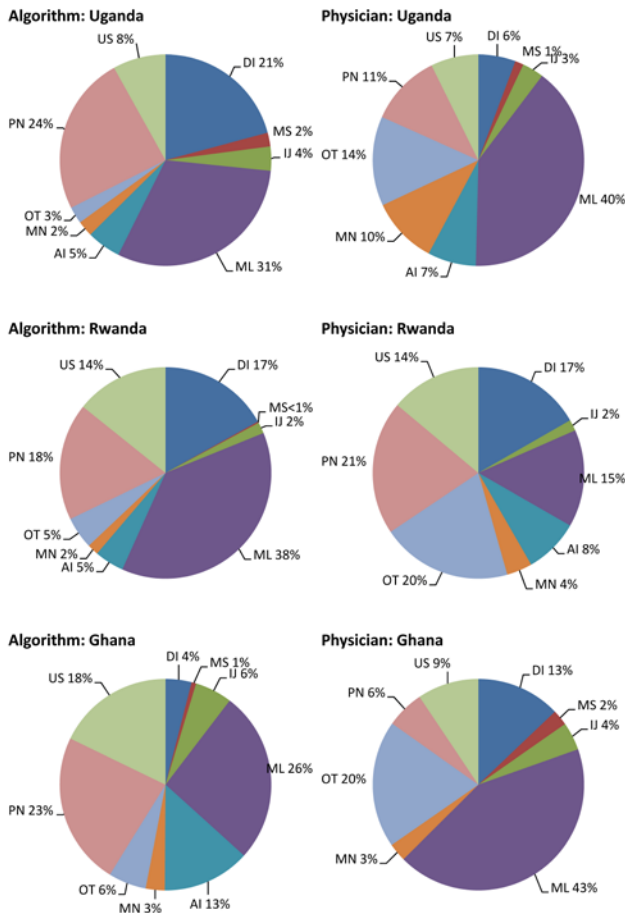
Figure 3. Cause specific mortality fractions among children aged 1–59 months by standardized computer algorithm and physician review, Uganda, Rwanda and Ghana. This figure includes side–by–side pie graphs to compare the cause specific mortality fractions among deaths of children 1–59 months generated by standardized computer algorithm and physician review in the three countries. DI – diarrhea; MS – measles; IJ – injury; ML – malaria; AI – AIDS; MN – meningitis; OT – other infections; PN – pneumonia; US – unspecified causes.

Table 4. Ranking of the top five single causes of deaths by age and ascertaining method, Uganda, Rwanda and Ghana

AGE GROUP	RANK	STANDARDIZED COMPUTER ALGORITHM	PHYSICIAN REVIEW
Uganda			
0–27 days	1	Intrapartum–related complications	Sepsis
	2	Preterm birth complications	Preterm birth complications
	3	Pneumonia	Intrapartum–related complications
	4	Tetanus	Tetanus
	5	Congenital abnormalities	Congenital abnormalities
1–59 months	1	Malaria	Malaria
	2	Pneumonia	Pneumonia
	3	Diarrhea	Meningitis
	4	AIDS	AIDS
	5	Injury	Diarrhea
Rwanda			
0–27 days	1	Intrapartum–related complications	Intrapartum–related complications
	2	Preterm birth complications	Sepsis
	3	Pneumonia	Pneumonia
	4	Congenital abnormalities	Preterm birth complications
	5	Tetanus	Diarrhea
1–59 months	1	Malaria	Pneumonia
	2	Pneumonia	Diarrhea
	3	Diarrhea	Malaria
	4	AIDS	AIDS
	5	Meningitis	Meningitis
Ghana			
0–27 days	1	Intrapartum–related complications	Intrapartum–related complications
	2	Preterm birth complications	Preterm birth complications
	3	Pneumonia	Congenital abnormalities
	4	Congenital abnormalities	Tetanus
	5	Tetanus	Sepsis
1–59 months	1	Malaria	Malaria
	2	Pneumonia	Diarrhea
	3	AIDS	Pneumonia
	4	Injury	Injury
	5	Diarrhea	Meningitis

The ranking of the top five single causes is show in **Table 4**. Despite discrepancies in the absolute values of CSMFs, the ranking of the top five single causes is similar within each age group across the three countries. Specifically, four out of the five leading causes are the same between results derived by the two approaches. In addition, the ranking is largely similar across countries.

DISCUSSION

In this paper, we derived comparable causes of child mortality distributions by applying an adapted standardized computer algorithm to re–analyze national VA data collected in Uganda, Rwanda and Ghana in 2007–2008. Overall, the distribution of child mortality is by and large similar across the three countries based on our results, with

malaria and pneumonia being the leading causes of under–five deaths and intrapartum–related complications and preterm birth complications being the major neonatal causes.

However, the distribution in Ghana appeared to be different from that in the other two countries in that the diarrhea–specific mortality fraction was much smaller, the AIDS–specific mortality fraction was larger, and more deaths were not assigned. We speculated that the differences between Ghana and the other two countries may be partially attributable to the measurement and data quality issues in the Ghana VA study. Only 2.5% of under–five deaths were assigned to diarrhea in Ghana, which was implausibly low compared to existing studies [6,39]. A closer

examination of the Ghana data and our diarrhea case definition revealed that although a large proportion of cases had diarrhea–related symptoms (34% in Ghana, compared to 45% in Uganda and 59% in Rwanda), only a small fraction of these cases had 6 or more stools on days when the symptoms were the most severe (17% in Ghana, compared to 52% in Uganda and 34% in Rwanda). We had no basis to believe that diarrhea symptoms differed between Ghana and the other two countries, and speculated that the discrepancy was partially caused by suboptimal data quality. The suspicion over data quality in Ghana may be further supported by the large AIDS–specific mortality fraction at 8.6%, which was implausibly high given an adult HIV prevalence of 1.8% in 2009 in Ghana [40]. The fact that a quarter of the under–five deaths were not assigned in Ghana, compared to 17% in Rwanda and 8% in Uganda, also raised the concern over quality of the Ghana VA study. One more explanation of the implausibly high AIDS fraction in Ghana could be the result of not assigning sickle–cell disease as a cause of death.

The kappa statistics showed substantial to poor agreement between results generated by the two ascertaining methods, suggesting that the individual–level agreement varied greatly by cause. Causes with more distinct signs and symptoms, such as injury, congenital malformation, preterm birth complications, and measles had a higher level of agreement compared to other causes. Malaria also had moderate agreement, which may be associated with its high prevalence. Other infectious causes like pneumonia, diarrhea, sepsis and AIDS all have fair to poor agreement, probably due to their non–specific symptoms and likely comorbidity with other infectious conditions. It is noted that the low specificity associated with infectious causes is not unique to computer algorithm, rather, it is a common issue shared by all methods ascertaining causes of death [41,42]. Poor agreement among some causes may also have something to do with the fact that we did not have access to the open narrative section of the VA studies. We could have missed useful information on symptoms and signs prior to death that physicians may have had access to [41]. However, the accuracy of causes ascertained at the individual–level is less of a concern as the purpose of the standardized computer algorithm is to derive comparable population–level distribution of child mortality.

The absolute values of CSMFs assigned by the standardized computer algorithm were fairly different from those assigned by physician review among neonates and children aged 1–59 months. However, when ranking of the leading five causes and their specific ranks were compared, many similarities can be drawn between results derived from the two approaches. It suggests that public health policy decisions could be largely similar based on distribution of causes of child mortality derived from both methods [36].

The study has several limitations. First, our preliminary child AIDS case definition has not been validated. The fact that the AIDS–specific fraction did not have a linear relationship with the adult HIV prevalence in the three countries could also suggest that our AIDS case definition have unsatisfactory validity. However, more specific signs and symptoms are generally required to improve the validity of the AIDS case definition. Additional efforts are urgently needed to develop and standardize AIDS case definition among children that can be used in national VA studies.
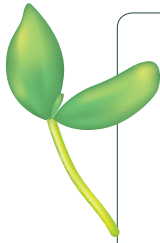
Second, the standardized computer algorithm assigned 38% of post–neonatal deaths to malaria in Rwanda, which is unlikely to be plausible. CHERG estimated that 3.7% of post–neonatal deaths were attributable to malaria in Rwanda in 2008 [6]. Another independent exercise by WHO applying a natural history model generated an even smaller fraction [43]. If the malaria–specific mortality burden was in fact low in Rwanda, the implausibly high malaria fraction assigned by the standardized computer algorithm was likely caused by the high misclassification error associated with low specificity of the malaria case definition and the low cause–specific fraction [25,44,45]. In fact, given the non–specific symptoms and the associated low specificity [46], concerns have been raised over the suitability of the application of VA to ascertain malaria in low prevalence settings [26,47,48].

In addition, neither the standardized computer algorithm nor physician review is capable of providing the "true" causes of death. Both approaches could be equally invalid. When the two approaches agree, it does not necessarily mean that there is greater truth to the causes assigned.

Despite these caveats, it is feasible to re–analyze national VA studies applying a standardized computer algorithm for the purposes of cross–country comparison and global burden of childhood disease estimation. The standardized computer algorithm produced internally consistent and comparable distribution of causes of child mortality in comparison to physician review. It also has the advantage of requiring minimal resources from the health care system. From the public health policy stand point of view, the standardized computer algorithm and physician review also generate similar sets of leading causes of child deaths. The standardized computer algorithm represents a promising way to re–analyze national or sub–national VA studies in place of physician review. It could be further strengthened with improved validity of child AIDS case definitions. The standardized computer algorithm should be of particular importance in sub–Saharan Africa, where human capital and financial shortfalls are the greatest. The application of a standardized computer algorithm on child VA data are one step forward toward the harmonization of cause–of–death reporting and estimation in children younger than five years. Among the

CHERG community, discussion is on–going about how to utilize national VA data so that consistent and comparable cause–of–death estimates can be generated across countries and time for the purpose of global burden of childhood disease estimation. We welcome a discussion on this subject among a wider community.

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Direct estimates of national neonatal and child cause–specific mortality proportions in Niger by expert algorithm and physician–coded analysis of verbal autopsy interviews

Henry D. Kalter[1], Abdoulaye–Mamadou Roubanatou[2], Alain Koffi[1], Robert E. Black[3]

[1] Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[2] Ministry of Health, Niamey, Niger

[3] The Institute for International Programs, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background This study was one of a set of verbal autopsy investigations undertaken by the WHO/UNCEF–supported Child Health Epidemiology Reference Group (CHERG) to derive direct estimates of the causes of neonatal and child deaths in high priority countries of sub–Saharan Africa. The objective of the study was to determine the cause distributions of neonatal (0–27 days) and child (1–59 months) mortality in Niger.

Methods Verbal autopsy interviews were conducted of random samples of 453 neonatal deaths and 620 child deaths from 2007 to 2010 identified by the 2011 Niger National Mortality Survey. The cause of each death was assigned using two methods: computerized expert algorithms arranged in a hierarchy and physician completion of a death certificate for each child. The findings of the two methods were compared to each other, and plausibility checks were conducted to assess which is the preferred method. Comparison of some direct measures from this study with CHERG modeled cause of death estimates are discussed.

Findings The cause distributions of neonatal deaths as determined by expert algorithms and the physician were similar, with the same top three causes by both methods and all but two other causes within one rank of each other. Although child causes of death differed more, the reasons often could be discerned by analyzing algorithmic criteria alongside the physician's application of required minimal diagnostic criteria. Including all algorithmic (primary and co–morbid) and physician (direct, underlying and contributing) diagnoses in the comparison minimized the differences, with kappa coefficients greater than 0.40 for five of 11 neonatal diagnoses and nine of 13 child diagnoses. By algorithmic diagnosis, early onset neonatal infection was significantly associated ($\chi^2 = 13.2$, $P < 0.001$) with maternal infection, and the geographic distribution of child meningitis deaths closely corresponded with that for meningitis surveillance cases and deaths.

Conclusions Verbal autopsy conducted in the context of a national mortality survey can provide useful estimates of the cause distributions of neonatal and child deaths. While the current study found reasonable agreement between the expert algorithm and physician analyses, it also demonstrated greater plausibility for two algorithmic diagnoses and validation work is needed to ascertain the findings. Direct, large–scale measurement of causes of death complement, can strengthen, and in some settings may be preferred over modeled estimates.

Correspondence to:

Dr. Henry Kalter
Department of International Health
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St., Suite E8132
Baltimore, MD 21205, USA
hkalter1@jhu.edu

Health policy makers and program planners require data on the levels and causes of death in order to identify health priorities, allocate sparse resources and evaluate health program impact. Death registration with medical certification of the cause of death is the best source of such data, but a minority of low and middle income counties (LMIC) have well–functioning vital registration systems with good population coverage, and in many countries a large proportion of deaths occur outside of medical care. In such settings, verbal autopsy interviews conducted in Demographic and Surveillance Sites [1], as part of a national survey [2], or in a few countries in nationally–representative sample registration systems [3], remains the best source of empirical data on causes of death.

A verbal autopsy (VA) inquiry of a child death consists of a retrospective interview on the signs and symptoms of the fatal illness with the mother or other main caregiver of the child. The cause of death is determined from pre–defined, expert–determined, combinations of the reported illness signs and symptoms (algorithms) or by independent classification of the VA interview findings by one or more physicians. The method has been directly validated against medical reference standard diagnoses and has been found to work best in identifying distinctive syndromes such as tetanus, measles and injuries and moderately well for less specific illnesses like pneumonia and malaria [4-9]. Newer, statistical and probabilistic analytic approaches have shown promise in increasing the validity of verbal autopsy diagnoses [10], but up till now these methods have not been directly compared to VA algorithms and agreement has not been reached on the best analysis method [11]. Also, widely accepted and user–friendly software needed to conduct statistical analyses of VA data has yet to be produced and made accessible.

As part of the Child Health Epidemiology Reference Group's (CHERG) recent effort to directly measure the causes and determinants of neonatal and child mortality in selected, high–priority countries, a national verbal/social autopsy (VASA) study was conducted in Niger. Niger was selected because its child mortality level is among the highest in the world, ranked number 10 in under–5 mortality [12]; because a recent national mortality survey demonstrated that there has been a significant decrease in under–5, but not neonatal, mortality; and because there were no previous reliable or large–scale direct measures of the causes of neonatal or child deaths in Niger. In addition to the concern of global public health practitioners, both the Ministry of Health of Niger and the UNICEF country office took a keen interest in the study and have utilized the findings in the development of improved maternal and child health policies and programs. This paper reports on the verbal autopsy findings of the VASA study.

METHODS

Study sample

The deaths included in the Niger VASA study were identified by the Niger National Mortality Survey (NNMS) conducted in July to August 2010. This survey used a two–stage random cluster design to select 25 024 households. A lifetime birth history was conducted for all women 15 to 49 years old in each sampled household to identify all live births and child deaths [13,14].

The VASA study sought to examine samples of the most recent 605 neonatal (0 to 27 days old) and 605 child (1 to 59–month olds) deaths, which, with alpha = 0.05, Z = 1.96, design effect = 1.4 and non–response rate = 0.1, are sufficient to achieve precision of ±0.05 around an assumed proportion of 0.50 for the most common cause of death in each age group. This required sampling deaths as far back from the survey period as four years, during which there were 734 neonatal deaths and 1646 child deaths. From these, starting with the most recent under–five years old death (whether it was a neonate or child) in all the households and moving back in time, we selected the one most recent under–five years old death (or one at random if there were two or more most recent deaths in the same month) in each household with at least one such death until we had achieved our desired sample sizes of 605 deaths in each age group. Comparing this method with selecting one death at random from each household in the same time period showed no substantial differences in the child's age at death or sex or in the respondent's age. We therefore took the most recent deaths in order to limit the recall period as much as possible, while maintaining the representativeness for each age group within the time period covered by the deaths in that group.

VASA interview

The VASA questionnaire developed for this study blends the Population Health Metrics Research Consortium (PHMRC) verbal autopsy questionnaire [15] with the CHERG social autopsy questionnaire [16]. The original English VASA questionnaire was translated to French and then from French to the two main languages of Niger, Haoussa and Zarma. Each Nigerien language questionnaire was independently back–translated to French to cross–check and reconcile the translations, and then scrutinized by a local anthropologist to ensure that appropriate local terms were used for the illness signs and symptoms.

The translated questionnaires were inserted into a CSProX [17] CAPI (computer–assisted personal interview) software application developed for the VASA studies, and the interviews were conducted and responses captured in the field directly on netbook computers. The software was designed

to minimize data entry errors by guiding the interviewer through the questionnaire and providing numerous real–time data checks and opportunities to correct internally inconsistent responses.

The VASA interviews were conducted as follow–up visits to the households with a death identified by the NNMS. Most of the fieldwork was conducted from March to April 2012. Revisits to 114 households to resolve discrepancies in the deceased children's birth and death dates determined by the VASA and NNMS extended the data collection until September 2012.

The interviewers were 12 women and eight men, all native speakers of Haoussa and/or Zarma, 86% of whom had some post–secondary education and the remaining had completed secondary school. They received 10 days of classroom training in the VASA study background, procedures, ethical standards and conduct of the interview on the netbook, followed by three days of field practice, all conducted in French, Haoussa and Zarma. Each of the seven teams of two to four interviewers and one supervisor was visited twice by an office supervisor during the 55 days of data collection to provide additional supervision and to collect interim copies of the data files for monitoring purposes.

The interviewers were trained to select as the respondent the person who most closely cared for the child during the fatal illness, which is typically, but not always, the child's mother. Secondary respondent(s) were allowed, if necessary, since the interview covered all phases of the illness and careseeking including, for neonatal deaths, the mother's pregnancy and delivery, during and after which she herself might have been ill and so less aware of the child's condition and illness events. In case of any disagreement between respondents, the main respondent's answer was always taken as final.

Development of verbal autopsy algorithms and hierarchies

The expert algorithms (EAVA) for neonatal and child causes of death used by this study (see **Online Supplementary Document**) utilized questions in the VA portions of the VASA questionnaire and one social autopsy question on the ordering of onset of the illness signs and symptoms. The algorithms were based on those developed by verbal autopsy researchers for prior VA validation studies [5-9], further consultation with additional verbal autopsy experts (GD and AB in acknowledgments), and a literature review to identify illness signs and symptoms commonly associated with particular neonatal and child illnesses [18-21]. Algorithms for some conditions included in this study have not been developed or tested in prior validation studies; new algorithms were developed for these conditions, in-

cluding neonatal jaundice, neonatal hemorrhagic syndrome, AIDS and hemorrhagic fever. The Pertussis algorithm was adapted from the US Centers for Disease Control and Prevention case definition [22].

Most algorithms were selected for their expected higher specificity than sensitivity in order to decrease false positives, as this characteristic minimizes misclassification error in the VA diagnosis of neonatal and child causes of death in developing countries [23]. Algorithms for possible pneumonia or acute respiratory infection (ARI), possible diarrhea, possible dysentery and possible malaria, all designed to have higher sensitivity than their corresponding probable diagnoses, were developed to claim these possible diagnoses from the unspecified cause of death group. The final cause of death distributions combined probable and their related, possible, diagnoses.

In addition to algorithms for neonatal and child causes of death, an algorithm for one maternal condition, infection before or during labor and delivery (see **Online Supplementary Document**), was developed to assess the association between maternal infection and early onset severe neonatal infection.

Hierarchies were developed for the neonatal and child diagnoses (see **Online Supplementary Document**) to select the EAVA primary cause of death for each child; the hierarchies also allowed for the identification of possible co–morbid causes. In addition, if a child had a diagnosis either as the primary or a co–morbid cause of death, then that was assigned as an overall 'algorithmic cause', which was compared to the overall physician–certified VA diagnoses as described below.

The ordering of the hierarchies was based mainly on principles incorporated in the ICD–10 rules of identifying the main disease or condition of the infant for early neonatal deaths (referred to in the ICD rules, together with stillbirths, as perinatal deaths, and recorded on a separate perinatal certificate), and for older infants and children the underlying cause of death, meaning the condition as a consequence of which the direct cause of death occurred [24]; and for some conditions to select the most severe or site–specific morbidity as the primary cause. The ICD–10 rules for perinatal deaths specify that the mode of death, including prematurity, should not be classified as the main disease or condition of the infant unless it was the only condition known. This rule was followed by placing preterm delivery at the bottom of the hierarchy for neonatal deaths, in order to select possible co–morbid conditions such as sepsis as the main disease or condition. An example of the underlying cause principle is that in the child hierarchy measles was placed above pneumonia because pneumonia is likely to have occurred as a consequence of mea-

sles in a child with both conditions; and of the severity or site–specific principle is that in the neonatal hierarchy meningitis was placed above sepsis because it identifies the focus of the infection.

This last example above also illustrates how the hierarchies identify possible comorbidity as well as the main or underlying cause of death. A neonate with meningitis would most likely also have sepsis; in such a case the hierarchy would first select meningitis, placed above sepsis, as the primary cause, and below would identify co–morbid sepsis. Diarrhea was placed above pneumonia in the hierarchies based on WHO's interpretation of the ICD–10 rule that pneumonia should be considered a consequence of conditions that impair the immune system [25]. Lastly, all possible diagnoses were placed below their corresponding probable diagnoses to detect possible cases that did not meet the probable cause criteria.

The hierarchies developed for this study differ somewhat from the standardized CHERG hierarchy developed for an earlier study that examined trends in the causes of child mortality in Bangladesh [26]. In addition to incorporating several conditions not included in the earlier hierarchy (for neonates: meningitis, neonatal jaundice, hemorrhagic disease of the newborn and sudden unexplained death; for 1 to 59–month olds: AIDS, dysentery, Pertussis, malaria and hemorrhagic fever), the current neonatal hierarchy moved preterm delivery below all other conditions in accordance with the ICD rule cited above, the child hierarchy moved malnutrition up in order to identify malnutrition as an underlying cause of death, and both the neonatal and child hierarchies identified diarrhea ahead of pneumonia, in keeping with WHO's interpretation of the ICD rule for coding pneumonia in the presence of conditions that impair immunity.

Physician cause of death assignment

One physician, a Nigerien neonatologist (A–MR), read the VA interviews and completed an international certificate of death for each neonatal and child death. Guidelines for classifying the cause of death from a VA interview, including minimal diagnostic criteria required for each cause (see **Online Supplementary Document**), were developed for the physician's use together with her clinical judgment and discussed in a three–hour training session. WHO standards for attributing cause of death from verbal autopsy [25] also were discussed during the training, and the physician was provided a copy of both documents. The physician completed several practice cases prior to starting the work, which were reviewed and discussed with her to help ensure proper filling of the death certificates.

The underlying cause of death, which is the antecedent cause on the lowest of lines 1a to 1d of section 1 of the filled

certificate, was taken as the physician–certified (PCVA) cause of death. Any other causes listed higher in the causal chain, as well as any contributing causes of death listed in section 2 of the certificate, also were recorded. For neonates, the physician also certified any maternal underlying and contributing causes of the neonatal death. Any maternal underlying causes (in section 1 of the death certificate) always were placed beneath the child cause(s). In such cases, the child cause lowest in lines 1a to 1c was taken as the underlying cause of death, and the maternal cause lowest in lines 1b to 1d was the underlying maternal cause. An example would be a neonatal death with birth asphyxia as the underlying cause of death in line 1a and obstructed labor as the underlying maternal cause in line 1b. Although a separate perinatal certificate was not utilized to classify neonatal deaths, the examples provided in the physician's guide and in the WHO VA standards manual make clear that preterm delivery should not be coded as the underlying cause of death when another condition is present.

All direct, antecedent and contributing child causes for each cause of death were combined into one overall 'physician cause' if the child had that diagnosis at any of the three levels, which was compared to the combined primary and co–morbid 'algorithmic cause' in order to assess the overall level of agreement between the algorithmic and physician diagnoses of the child causes of death.

Meningitis surveillance data

Surveillance data on all–ages meningitis cases and deaths in 2007 to 2010, stratified by the country's eight regions, were available from the Niger Ministry of Health's Centre for Medical Research and Health, which works closely with the Institute Pasteur. These data were used to conduct an ecological plausibility check of the VA diagnoses of child meningitis deaths. The surveillance data for 2007 to 2009, during which 86% of the total 21 898 cases occurred, included the number of cases notified, the number for which the public health laboratory received a cerebrospinal fluid (CSF) sample, and the number of samples with a positive bacterial culture. The 2010 data included only the number of cases notified.

Statistical analyses

The EAVA diagnostic criteria and hierarchies were computerized to automate the determination of the distributions of neonatal and child primary causes of death and possible co–morbid causes from the VA interview responses. The PCVA diagnoses of direct, underlying and contributing causes of death were directly entered into the computer.

The rank ordering of EAVA primary causes of death and PCVA underlying causes was separately compared for the neonatal and child deaths. Differences between the mortal-

ity proportions for each EAVA primary cause of death and PCVA underlying cause of death were evaluated with the mid–p chi–square test of proportions [27] and by examining the overlap of their 95% confidence intervals. The level of agreement beyond that due to chance alone between the combined 'algorithmic cause' and the overall 'physician cause' of death diagnoses was assessed with the Kappa statistic [28] in order to evaluate the degree to which differences in the primary EAVA and PCVA diagnoses were due to the ordering of the diagnoses by the EAVA hierarchy and the physician. The chi–square statistic was used to evaluate the association between maternal infection and early onset severe neonatal infection, including meningitis, pneumonia and sepsis separately and combined. All statistical analyses were performed using SAS version 9.2 for Windows [29]. Because the deaths analyzed in this study were identified by the NNMS, the survey sample cluster weights were applied to all analyses, including determination of the EAVA and PCVA cause–specific mortality proportions, the level of agreement between the EAVA and PCVA diagnoses, and the associations between maternal infection and early onset neonatal infection.

The relationship between the geographic distributions of EAVA and PCVA child meningitis deaths and all–ages meningitis surveillance cases and deaths was examined by comparing the VA–diagnosed region–meningitis–specific proportional mortality for 1 to 59–month old children to the percentage of the entire country's surveillance–detected all–ages meningitis cases and deaths in each region. We examined the child VA meningitis–specific proportional mortality in each region instead of the percent of all child VA meningitis deaths that occurred in each region because, just as for the surveillance data, this could be influenced by the regional population distribution (**Table 1**), ie, given similar attack rates, the more people in a region, the more cases and deaths from any particular cause might be expected. This assessment examined only the primary EAVA and underlying PCVA cause of death since the purpose was to

evaluate the meningitis diagnoses that could be reported for vital statistics purposes.

Ethics approval

The study was approved by the National Consultative Ethics Committee of the Niger Ministry of Health and by the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health. All the study personnel received training in ethical principles and practices for human subjects research, and informed consent was given by all study participants before the VASA interview was conducted.

RESULTS

The final VASA sample consisted of 1166 (96.9%) completed interviews of 1203 attempted, including 453 neonatal deaths, 620 child deaths and 93 stillbirths. The 93 stillbirths derived from the VASA interviews determining that these (primarily) neonatal deaths of live born children identified by the NNMS were in fact stillbirths. Because the NNMS was not designed to detect stillbirths, and so these deaths do not constitute a representative sample of stillbirths, they were not included in the current analysis. In addition to the live births identified by the NNMS that were determined by the VASA to be stillbirths, some additional cases moved between the neonatal and child age groups. These were double–checked during revisits to the affected households. The final VASA–determined birth status and age at death were taken as the correct data for this study. **Table 1** shows the geographic distribution of the neonatal and child deaths.

The interview recall periods (from death till the VASA interview) for the neonatal and child deaths were, respectively, 2 to 5 years (mean=3.51, standard deviation=1.06 years) and 2 to 5 years (mean=2.69, standard deviation=0.88 years). Three–hundred eleven (68.7%) of the 453 neonates died before attaining seven days of age. Of the 620 children, 269 (43.4%) died at age 1 to 11 months, 144 (23.2%) at 12 to 23 months old, and 207 (33.4%) at age 24 to 59 months.

Neonatal deaths

Causes of death. Table 2 shows the EAVA primary and possible co–morbid causes of death of the 453 neonates. Taking sepsis, pneumonia and meningitis together, the primary cause of death of 240 (53.2%) of the neonates was a severe infection. Another 18 (4.0%) died from tetanus and 26 (5.7%) from diarrhea. After infectious causes, the next leading primary condition was birth injury and/or asphyxia, causing 90 (19.9%) of the deaths. Preterm delivery was the primary cause of death of only 12 (2.7%) of the neonates; and including all cases with either primary or co–

Table 1. Distribution of the verbal–social autopsy deaths (VASA), by region of Niger

| Region	2007–2010 population	Neonatal deaths	Child deaths	Total
			VASA CASES	
Agadez	420 026	21	8	29
Diffa	472 799	43	43	86
Dosso	1 944 322	81	116	197
Maradi	2 942 972	79	94	173
Tahoua	2 536 713	51	104	155
Tillabéri	2 416 875	84	95	179
Zinder	2 683 738	76	151	227
Niamey	954 613	18	9	27
Total	14 372 058	453	620	1073

morbid preterm, only 41 (9.1%) of the newborns had pre-term delivery as a cause of death. The EAVA analysis was not able to classify the cause of death for 42 (9.2%) of the neonates.

Table 2 also demonstrates a high degree of possible comorbidity, with sepsis being the most common co–morbid condition, particularly found in most deaths caused by birth asphyxia and in all cases of meningitis, pneumonia and diarrhea. Preterm delivery was another common co–morbid condition, occurring in 17 cases of primary sepsis and 9 of birth asphyxia.

Figure 1 shows the neonates' EAVA primary causes of death and PCVA underlying causes of death. Leaving aside deaths with an unspecified diagnosis, both methods ranked sepsis, birth injury/asphyxia and pneumonia, respectively, as causes 1, 2 and 3, and all but two other causes (diarrhea

and other) were within one rank of each other. While the relative proportions of the causes and the overall pictures are quite similar, **Table 3** reveals some substantial differences in the proportion of deaths due to several individual causes. Severe neonatal infections predominated by both analytic methods, with each identifying more sepsis than pneumonia and more pneumonia than meningitis. The largest difference was in the higher overall percentage of severe infections diagnosed by PCVA (64.4%) compared to EAVA (53.2%), and the correspondingly lower percentage of PCVA diarrhea and tetanus deaths (combined, 0.8% vs 9.7% for the algorithms). Also, PCVA failed to classify the cause of 6.0% of the deaths, compared to 9.2% for EAVA.

Table 4 shows the level of agreement between the combined 'algorithmic cause' and overall 'physician–cause' of death for each diagnosis. There was excellent agreement,
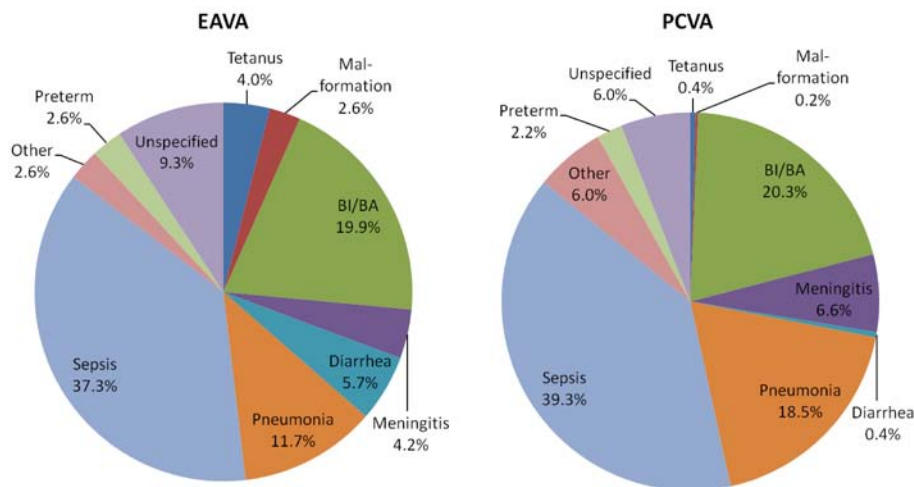
Figure 1. Verbal autopsy expert algorithm, hierarchical primary and physician–certified underlying causes of 453 neonatal deaths, Niger, 2007–2010. EAVA – expert algorithm verbal autopsy, PCVA – physician–certified verbal autopsy. Other: EAVA – 1 neonatal jaundice, 1 hemorrhagic disease of the newborn, 10 sudden unexplained death; PCVA – 3 neonatal jaundice, 12 sudden unexplained death, 12 refuse to suck.

Table 2. Expert algorithm, hierarchical verbal autopsy primary and possible co–morbid causes of 453 neonatal deaths, Niger, 2007–2010

EAVA PRIMARY CAUSE OF DEATH (POSSIBLE CO–MORBID CAUSES)	N	%
Neonatal tetanus (5 BI/BA, 3 diarrhea, 3 pneumonia)	18	4.0
Congenital malformation (8 BI/BA, 1 meningitis, 1 diarrhea, 3 pneumonia, 2 preterm, 9 sepsis)	12	2.7
Birth injury (9) and/or asphyxia (85) (6 meningitis, 1 diarrhea, 34 pneumonia, 9 preterm, 78 sepsis, 2 hemorrhagic disease)	90	19.9
Meningitis (14 pneumonia, 19 sepsis)	19	4.2
Diarrhea (4 pneumonia, 26 sepsis)	26	5.7
Pneumonia (53 sepsis)	53	11.6
Sepsis (17 preterm)	169	37.4
Neonatal jaundice	1	0.2
Hemorrhagic disease of the newborn	1	0.3
Sudden unexplained death (1 preterm)	10	2.1
Preterm delivery (7 with Respiratory Distress Syndrome)	12	2.7
Unspecified	42	9.2

EAVA – expert algorithm verbal autopsy, BI/BA – birth injury and/or birth asphyxia

Table 3. Expert algorithm– and physician–diagnosed primary cause of death mortality proportions, 95% confidence limits, chi–squares and p–values for 453 neonatal deaths, Niger, 2007–2010

DIAGNOSIS	EAVA (%)	95% CL*	PCVA (%)	95% CL*	χ^2	P
Neonatal tetanus	4.0	2.4, 6.1	0.4	0.1, 1.5	13.1	<0.001
Malformation	2.6	1.4, 4.5	0.2	0.01, 1.1	9.4	0.002
Birth injury and/or asphyxia	19.9	16.4, 23.7	20.3	16.8, 24.2	0.03	0.860
Meningitis	4.2	2.6, 6.4	6.6	4.6, 9.2	2.6	0.106
Diarrhea	5.7	3.9, 8.2	0.4	0.1, 1.5	21.2	<0.001
Pneumonia	11.5	8.8, 14.7	18.5	15.2, 22.3	8.9	0.003
Sepsis	37.3	32.9, 41.8	39.3	34.9, 43.9	0.4	0.538
Sepsis + Pneumonia + Meningitis	53.0	48.4, 57.6	64.4	60.0, 68.8	12.3	<0.001
Other†	2.6	1.4, 4.5	6.0	4.0, 8.4	6.0	0.014
Preterm	2.7	1.4, 4.5	2.2	1.1, 3.9	0.2	0.666
Unspecified	9.3	6.9, 12.2	6.0	4.0, 8.4	3.5	0.060

EAVA – expert algorithm verbal autopsy, PCVA – physician–certified verbal autopsy

*Mid–p 95% confidence limits.

†Other: neonatal jaundice, hemorrhagic disease of the newborn and sudden unexplained death.

Table 4. Agreement of all combined expert algorithm verbal autopsy (VA) primary and possible co–morbid diagnoses with all combined physician–certified VA direct, underlying and contributing causes of 453 neonatal deaths, Niger, 2007–2010

DIAGNOSIS EAVA / PCVA	EAVA	PCVA	AGREE +	AGREE –	KAPPA†	95%CL*
Tetanus / Tetanus	18	8	2	429	0.10	–0.07, 0.28
Malformation / Malformation	12	11	7	436	0.56	0.31, 0.80
Birth injury and/or asphyxia / BI/BA*	103	113	84	321	0.71	0.63, 0.78
Meningitis / Meningitis	26	34	9	402	0.24	0.09, 0.40
Diarrhea / Diarrhea	31	24	20	418	0.71	0.57, 0.85
Pneumonia / Pneumonia	110	87	48	305	0.35	0.25, 0.45
Sepsis / Sepsis	354	185	171	86	0.22	0.15, 0.28
Jaundice / Jaundice	3	11	2	441	0.28	–0.03, 0.59
Sudden death / Sudden death	10	12	10	441	0.88	0.74, 10.0
Preterm / Preterm	41	32	31	410	0.82	0.72, 0.92
Preterm / Refuse to suck	41	19	7	400	0.20	0.05, 0.35
Unspecified / Unspecified	42	28	13	396	0.32	0.17, 0.47

EAVA – expert algorithm verbal autopsy, PCVA – physician–certified verbal autopsy, Bi/BA – birth injury and/or asphyxia

*Mid–p 95% confidence limits.

†Kappa agreement: Less than chance ≤0, Slight ≤0.20, Fair ≥0.21, Moderate ≥0.41, Good ≥0.61, Excellent ≥0.81.

with a kappa greater than 0.80, for two of the 11 causes, good agreement, with a kappa greater than 0.60, for two causes, moderate agreement, with a kappa greater than 0.40, for one cause, and fair agreement, with a kappa greater than 0.20, for three causes. Only two causes (tetanus and jaundice) had less than chance agreement, with the lower 95% confidence limit below 0.

Association of neonatal severe infection and maternal sepsis. Table 5 demonstrates a positive association between early onset severe neonatal infection as the primary cause of neonatal death and maternal infection, both diagnosed by EAVA. The strongest relationship between neonatal and maternal infection was for all (meningitis, pneumonia and sepsis) early onset severe neonatal infections combined compared to all later onset severe neonatal infections ($\chi^2 = 13.20$, $P = 0.0003$); and the weakest was for early onset pneumonia compared to later onset pneumonia. The association between early onset neonatal infection and maternal infection also was significant when compar-

Table 5. Relationship of maternal sepsis during pregnancy or delivery and early onset severe neonatal infection as the primary cause of death for 453 neonatal deaths in Niger, 2007–2010

EAVA CAUSE OF DEATH (MATERNAL SEPSIS, MS)	N	%	χ^2, P
Meningitis (6 with maternal sepsis)	19	4.2	
Illness onset <2 d (MS: 5 [60.3%])	8	1.8	5.67, 0.017
Illness onset ≥2 d (MS: 1 [9.3%])	11	2.4	
Pneumonia (14 with maternal sepsis)	53	11.6	
Illness onset <2days (MS: 7 [30.3%])	23	5.1	0.15, 0.701
Illness onset ≥2 d (MS: 8 [25.6%])	30	6.6	
Sepsis (25 with maternal sepsis)	169	37.4	
Illness onset <2 d (MS: 17 [26.1%])	65	14.2	11.08, 0.001
Illness onset ≥2 d (MS: 8 [7.5%])	105	23.2	
Severe neonatal infection (MS: 45 [18.7%])	241	53.2	
Illness onset <2 d (MS: 28 [30.0%])	95	21.0	13.20, <0.001
Illness onset ≥2 d (MS: 17 [11.3%])	146	32.2	
All neonatal deaths (MS: 93 [20.6%])	453	100.0	
Severe infection onset <2 d (MS: 28 [30.0%])	95	21.0	6.45, 0.011
All other deaths (MS: 65 [18.1%])	358	79.1	

EAVA – expert algorithm verbal autopsy

ing early onset infections to all other causes of neonatal death ($\chi^2 = 6.45$, $P = 0.011$).

Child deaths

Causes of death. Table 6 shows the EAVA primary and possible co–morbid causes of death of the 620 children aged 1 to 59 months. Malaria was the leading cause, followed by diarrhea and meningitis. Pneumonia placed a distant fourth, followed by dysentery and AIDS. Together, these six major infectious causes were responsible for 543 (87.6%) of the child deaths. Injuries caused only 6 (0.9%) deaths, and unspecified causes accounted for 28 (4.5%) deaths. Malnutrition was the underlying cause of only 14 (2.3%) deaths, but including its role as a co–morbid condition, malnutrition contributed to 145 (23.4%) of the deaths.

As with the neonates, **Table 6** also demonstrates a high degree of possible comorbidity. However, while sepsis was the predominant co–morbid condition for neonates, in children co–morbidity of pneumonia and diarrhea with primary meningitis, and between malaria, diarrhea and pneumonia were most important.

Figure 2 shows the children's EAVA primary causes of death and PCVA underlying causes of death. Unlike for the neonates, the ranks of no leading EAVA and PCVA causes exactly matched each other, although two, malaria and pneumonia, came within one rank of each other and meningitis was ranked number 3 by EAVA and 1 by PCVA. At the low end, EAVA and PCVA both ranked injury, hemorrhagic fever and other, respectively, at number 9, 10 and 12. It was in the middle ground that the two methods most disagreed with each other, with combined diarrhea/dysen-

Table 6. Expert algorithm, hierarchical verbal autopsy primary and possible co–morbid causes of 620 child deaths, Niger, 2007–2010

EAVA PRIMARY CAUSE OF DEATH (POSSIBLE CO–MORBID CAUSES)	N	%
Injury (2 malaria)	6	0.9
AIDS (12 meningitis, 7 dysentery, 9 diarrhea, 1 pertussis, 17 pneumonia, 3 malaria)	17	2.8
Malnutrition (1 meningitis, 3 malaria, 3 diarrhea, 2 pneumonia)*	14	2.3
Measles (3 meningitis, 2 dysentery, 4 diarrhea, 4 pneumonia, 2 malaria)	9	1.4
Meningitis (18 dysentery, 56 diarrhea, 8 pertussis, 56 pneumonia)	113	18.3
Dysentery (10 pneumonia, 7 malaria)	39	6.3
Diarrhea (40 pneumonia, 11 malaria)	121	19.5
Pertussis (2 pneumonia, 2 malaria)	2	0.3
Pneumonia (3 dysentery, 6 diarrhea, 14 malaria)	73	11.8
Malaria (8 dysentery, 20 diarrhea, 40 pneumonia)	180	28.9
Hemorrhagic fever	5	0.9
Other infections	13	2.1
Unspecified	28	4.5

EAVA – expert algorithm verbal autopsy
*131 additional cases with co–morbid malnutrition.

tery off by five ranks, the order of measles and malnutrition reversed at ranks 6 and 8, and other infections and AIDS off, respectively by three and five ranks. Several apparent marked differences in the EAVA and PCVA proportions were confirmed by the statistical measures in **Table 7**. Malaria and pneumonia together caused, respectively, 40.8% and 35.0% of the EAVA and PCVA deaths, while the EAVA and PCVA malaria proportions alone differed markedly. There were large differences as well for several other diagnoses, with the most notable disparities being that EAVA identified more diarrhea (19.5% vs 2.3% for PCVA) and
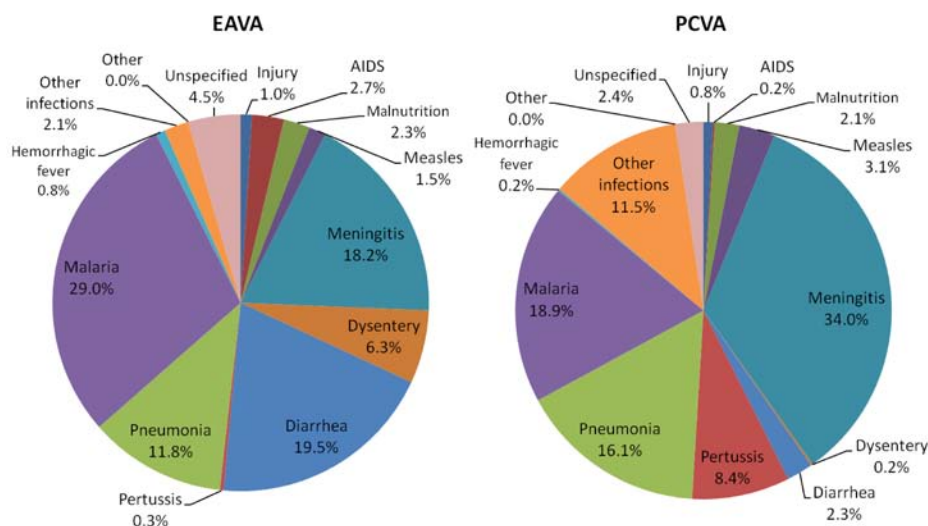
Figure 2. Verbal autopsy expert algorithm, hierarchical primary and physician–certified underlying causes of 620 child deaths, Niger, 2007–2010. EAVA – expert algorithm verbal autopsy, PCVA – physician–certified verbal autopsy.

dysentery (6.3% vs 0.2%), while PCVA diagnosed more meningitis (34.0% vs 18.2% for EAVA), other infections (11.5% vs 2.1%) and Pertussis (8.4% vs 0.3%).

Table 8 displays the level of agreement between the combined 'algorithmic cause' and overall 'physician–cause' of death for each diagnosis. There was excellent agreement, with a kappa greater than 0.80, for dysentery, and good agreement, with a kappa greater than 0.60, for diarrhea, both of whose levels as the main cause diverged substantially; as well as good agreement for three additional causes. Four causes had a kappa greater than 0.40, indicating moderate agreement, including pneumonia and meningitis, whose EAVA and PCVA levels as the main cause differed so

greatly. Measles and malaria had fair agreement, with a kappa greater than 0.20. Only two causes (Pertussis and other infections) had less than chance agreement, with the lower 95% confidence limit below 0. The kappa measurements at the bottom of **Table 8** show fair to good agreement between some related EAVA and PCVA diagnoses that provide insight into some of the differences in the two methods' selections of primary and underlying causes of death.

Geographic distribution of surveillance and VA meningitis. Figure 3 displays the percent of all meningitis cases and deaths identified by the Niger public health surveillance system from 2007 to 2010 in each of the country's eight regions. The public health laboratory received a CSF

Table 7. Expert algorithm– and physician–diagnosed primary cause of death mortality proportions, 95% confidence limits, chi–squares and p–values for 620 child deaths, Niger, 2007–2010

Diagnosis	EAVA (%)	95%CL*	PCVA (%)	95% CL*	χ^2	P
Injury	1.0	0.4, 2.0	0.8	0.3, 1.8	0.10	0.762
AIDS	2.7	1.7, 4.3	0.2	0.0, 0.8	14.4	<0.001
Malnutrition	2.3	1.3, 3.7	2.1	1.2, 3.5	0.04	0.846
Measles	1.5	0.7, 2.6	3.1	1.9, 4.7	3.70	0.056
Meningitis	18.2	15.3, 21.4	34.0	30.4, 37.8	40.1	<0.001
Dysentery	6.3	4.6, 8.4	0.2	0.0, 0.8	37.3	<0.001
Diarrhea	19.5	16.5, 22.8	2.3	1.3, 3.7	95.2	<0.001
Pertussis	0.3	0.1, 1.1	8.4	6.4, 10.8	48.4	<0.001
Pneumonia	11.8	9.4, 14.5	16.1	13.4, 19.2	4.9	0.027
Malaria	29.0	25.6, 32.7	18.9	15.9, 22.1	17.6	<0.001
Malaria + Pneumonia	40.8	37.0, 44.7	35.0	31.3, 38.8	4.4	0.035
Hemorrhagic fever	0.8	0.3, 1.8	0.2	0.0, 0.8	1.5	0.220
Other infections	2.1	1.2, 3.5	11.5	9.1, 14.1	43.0	<0.001
Other	0.0	0.0, 0.5	0.0	0.0, 0.5	0.0	1.000
Unspecified	4.5	3.1, 6.4	2.4	1.4, 3.9	4.1	0.044

EAVA – expert algorithm verbal autopsy, PCVA – physician–certified verbal autopsy
*Mid–p 95% confidence limits.

Table 8. Agreement of all combined expert algorithm VA primary and possible co–morbid diagnoses with all combined physician–certified VA direct, underlying and contributing causes of 620 child deaths, Niger, 2007–2010

Diagnosis EAVA / PCVA	EAVA	PCVA	Agree +	Agree −	Kappa*	95%CL†
Injury / Injury	6	10	4	609	0.56	0.25, 0.86
AIDS / AIDS	17	10	8	600	0.55	0.32, 0.77
Malnutrition / Malnutrition	145	130	107	451	0.71	0.64, 0.78
Measles / Measles	9	31	6	586	0.28	0.09, 0.46
Meningitis / Meningitis	129	234	128	385	0.59	0.53, 0.66
Dysentery / Dysentery	76	58	58	544	0.85	0.78, 0.91
Diarrhea / Diarrhea	220	189	151	363	0.61	0.55, 0.68
Pertussis / Pertussis	11	64	4	550	0.09	−0.01, 0.19
Pneumonia / Pneumonia	242	143	123	358	0.49	0.42, 0.56
Malaria / Malaria	223	117	87	367	0.35	0.28, 0.43
Hemorrhagic fever / Hem. fever	29	18	15	588	0.62	0.45, 0.78
Other infections / Other infections	122	71	4	431	− 0.12	−0.17,−0.07
Unspecified / Unspecified	28	17	15	590	0.66	0.49, 0.82
Possible malaria / Malaria	91	117	79	490	0.71	0.64, 0.78
Other infections / Meningitis	122	234	99	362	0.40	0.32, 0.47

EAVA – expert algorithm verbal autopsy, PCVA – physician–certified verbal autopsy;
*Kappa agreement: Less than chance ≤0, Slight ≤0.20, Fair ≥0.21, Moderate ≥0.41, Good ≥0.61, Excellent ≥0.81.
†Mid–p 95% confidence limits.
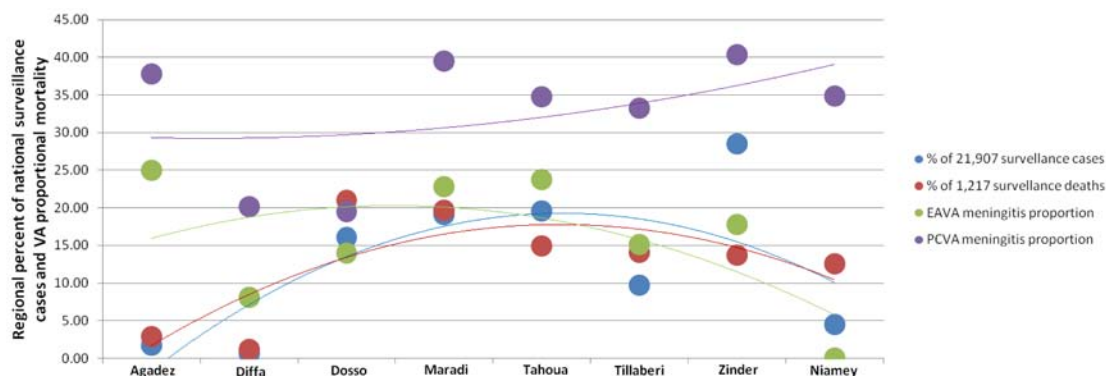
Figure 3. Meningitis surveillance cases and deaths, and verbal autopsy expert algorithm hierarchical primary and physician certified underlying meningitis deaths, Niger, 2007–2010.

sample for 41 percent of the 18 873 cases in 2007 to 2009, of which 45 percent grew out a positive bacterial culture. The pattern was similar by region, suggesting that the surveillance data provide an accurate measure of the distribution of meningitis in Niger during the period of the VA study. **Figure 3** also shows the EAVA– and PCVA–determined meningitis–specific proportional mortality of child deaths in each region identified by the NNMS from 2007 to 2010.

The surveillance data are for all ages, while the VA data are only for children. Also, the surveillance data come from a passive system, while the VA data are for deaths actively identified by a representative household survey. Therefore, it should not be expected to find perfect confluence between the two data sources. Nevertheless, **Figure 3** demonstrates a positive association between the surveillance data and the EAVA findings. The only strongly aberrant data point is for Agadez, where the NNMS detected only eight all–cause child deaths, two of which were EAVA–assessed as due to meningitis. **Figure 3** does not show a relationship between the surveillance data and PCVA meningitis diagnoses.

DISCUSSION

This verbal autopsy study was conducted as part of CHERG's effort to directly measure the causes of neonatal and child deaths in several high priority sub Saharan African countries to improve national, regional and global estimates that currently are based mainly on statistical models. This was the first national level CHERG VASA study to be undertaken. The deaths were identified by complete birth histories administered to all women aged 15 to 49 years participating in a national household survey; and, as such, constitute representative samples of neonatal and child deaths during the study's reference period of 2007 to

2010 from which direct measurements of the causes of death can be made without utilizing a modeling approach.

We conducted verbal autopsy interviews of the deaths and used two analytic methods to determine the causes of death, including VA expert algorithms arranged in a hierarchy to select the primary cause while simultaneously identifying possible co–morbid diagnoses, and physician certification to determine the underlying, direct and contributing causes of death.

For neonatal deaths, the two analytic methods provided broadly similar pictures of the cause proportions of mortality, with severe neonatal infections predominating over other causes, followed by birth asphyxia. Other causes played a less important role according to both methods, although EAVA distinguished more of the less common causes such as diarrhea, tetanus and malformations, while PCVA gave correspondingly greater prominence to severe infections.

The two methods provided more varied pictures of the causes of child deaths. The considerable difference found in the malaria proportions, together with the more similar proportion for malaria combined with pneumonia, could be due to the overlap in the clinical presentations of these conditions [30], with varying interpretation of the findings by the two VA methods. Diarrhea and dysentery were more common by the EAVA method, while meningitis, other infections and Pertussis were more prominent according to PCVA.

The order in which EAVA diagnoses are arranged in a hierarchy can strongly affect the distribution of the causes of death [31]. The hierarchy for the current study was arranged with two principles in mind—first, for early neonatal deaths and for all others, respectively, to identify the main disease or condition of the neonate and the underlying cause of death, which is the cause reported in international mortality

statistics; and when this may not be possible, such as when choosing between co–morbid pneumonia and meningitis, to select the cause that typically results in the more severe illness and so is more likely to kill or has the more specific syndrome and so more certain diagnosis. Thus, the aim was to duplicate as closely as possible the causes of death that would be reported according to ICD–10 rules.

Expert algorithms arranged in a hierarchy have been used in several recent national and sub–national verbal autopsy studies of the major causes of neonatal and child deaths [2,26,32,33]. Although the hierarchies for the current study were developed independently of those used by prior studies, there are several similarities between them. This underscores the attention to similar principles likely paid in developing the past and current hierarchies.

For neonatal deaths, one major difference is that the earliest hierarchy, from the 2004 Bangladesh Demographic and Health Survey (DHS) [2], like the current study and in accordance with ICD–10 rules, placed serious infections above preterm delivery, whereas the other studies placed preterm above serious infections or sepsis [26,32], with the study from India even placing preterm above birth asphyxia [33]. Absent other factors, then, all but the Bangladesh DHS study would be expected to find a higher proportion of preterm delivery as the main cause of death than the current study. Unlike the earlier studies, the current study also included meningitis, neonatal jaundice, hemorrhagic disease of the newborn and sudden unexplained death, as we sought to examine whether VA can reliably make these diagnoses when examining all major causes of neonatal death.

The past and current studies' hierarchies for child deaths also are broadly similar, though the current study again attempted to diagnose conditions not previously examined, including AIDS, underlying malnutrition, dysentery, Pertussis, malaria and hemorrhagic fever. Lastly, both the neonatal and child hierarchies placed diarrhea ahead of pneumonia to keep with WHO interpretation of the ICD coding rule for classifying these conditions when co–morbid.

The physician's goal when completing a death certificate is to select the main or underlying cause of death, as well as to identify the direct and contributing causes. In part 3 of the certificate the physician denotes the timing of the onset of each cause prior to death, with each antecedent cause required to precede the diagnoses above it, and the underlying cause, on the lowest line, required to be the most distal in onset. This offers a theoretical advantage to the PCVA method; however, few of the VA questions provide information on the timing of the illness sign or symptom's onset. Therefore, in cases with comorbidity the physician's judgment plays a large role in the ordering of the causes on the certificate and hence the designation of the underlying cause of death.

Despite all the potential sources of variability in the EAVA and PCVA diagnoses, as mentioned above the two methods identified broadly similar cause distributions for the neonatal deaths and several similarities for the child deaths. This is likely due, first, to the requirement that the physician utilize predetermined minimum diagnostic criteria, thereby imposing some measure of objectivity and standardization on the physician's diagnoses, similar to this aspect of the expert algorithms, and second, that the EAVA hierarchies were arranged as much as possible according to the same ICD rules that the physician was to follow in filling the death certificates. PCVA analysis has not always included required minimum diagnostic criteria nor completion of a death certificate, which might help explain the large differences found by some other studies between PCVA diagnoses and those reached by other methods [10,34].

For neonates, PCVA diagnosed more sepsis, pneumonia and meningitis than did EAVA. The placement of meningitis and pneumonia above sepsis in the hierarchy decreased the number of primary sepsis cases diagnosed by EAVA, but this does not explain the lower number of EAVA meningitis and pneumonia cases. PCVA meningitis required, at the minimum, the presence of bulging fontanelle or convulsions, while in addition the algorithm required lethargy or unconsciousness. This would tend to lower the number of EAVA meningitis cases. Regarding the greater proportion of deaths classified by EAVA as due to diarrhea, the kappa for all diarrhea diagnoses was 0.71 (95% CL: 0.57, 0.85), indicating good overall agreement between the two methods and suggesting that much of the difference was due to the methods' varied selection of the primary cause. This appears to be true for several other conditions as well, as there was a moderate or good kappa level of agreement between the combined algorithmic and physician diagnoses for nearly half the neonatal causes of death.

Much the same can be said for the differences in the EAVA primary causes and PCVA underlying causes of child deaths. Overall, there was moderate or good agreement between nine of the 13 causes, indicating that many of the differences were due to the selection of the main cause from among all the diagnoses reached by each method. Nevertheless, closer inspection reveals additional reasons for some of the differences. PCVA pneumonia required at least difficult or fast breathing, while the EAVA required minimum durations for these same illness signs; and even EAVA 'possible pneumonia' required additional criteria. Hence, a possible explanation for the larger number of PCVA pneumonia cases is that the physician often diagnosed pneumonia based on the minimum criteria alone. On the other hand, EAVA may have over–diagnosed malaria, given that several of these cases were 'possible malaria' (fever and no other VA infectious diagnosis). However, this is balanced

by the higher kappa level of agreement of PCVA malaria with EAVA possible malaria than with EAVA malaria, which can only be due to many of the physician's malaria diagnoses having been based solely on the presence of the minimum required criterion of fever.

The high PCVA meningitis proportion seems likely to be in excess, since its moderate kappa level of agreement with EAVA other infections shows that several PCVA meningitis diagnoses were based on the only overlapping required illness sign, convulsions. This was in addition to the many PCVA meningitis diagnoses that agreed with EAVA meningitis, which required stiff neck or bulging fontanelle. This conclusion is supported by the comparison of the geographic distributions of EAVA and PCVA meningitis to that of the meningitis surveillance data, which showed that EAVA meningitis closely paralleled the surveillance findings while the PCVA levels were consistently higher than the surveillance data. This ecologic assessment also served as a plausibility check of the EAVA child meningitis diagnoses and suggests that the EAVA can provide an accurate estimate of the meningitis–specific proportional mortality of children.

The significant positive association between EAVA maternal infection and early onset neonatal infection strengthens the plausibility of the EAVA diagnosis of severe neonatal infection. It is telling that this relationship held for early onset meningitis, sepsis and all severe infections combined, but not for early onset pneumonia, since it is known from validation studies that pneumonia is one of the more difficult neonatal diagnoses to make by verbal autopsy [8,10,35]. We are not aware of any prior verbal autopsy study that similarly examined such internal associations, thereby strengthening the credibility of the EAVA diagnoses. This plausibility analysis was not deemed feasible for the same PCVA diagnoses due to the inherent risk of bias in the physician finding maternal sepsis whenever early onset neonatal sepsis was diagnosed.

This highlights one potential advantage of EAVA over PCVA, which is its total objectivity and absolute consistency in applying its pre–defined diagnostic criteria [36]. This also might help explain why EAVA identified more of the less common neonatal diagnoses than did PCVA, that is, due to its total objectivity EAVA is open to all possible diagnoses for each case. The physician's perspective also can be seen in the small number of child diarrhea and dysentery deaths that were diagnosed. Though it's not possible to categorically state from this study which of the diarrhea estimates is more accurate, the PCVA value of 2.5% is far below the most recent CHERG modeled estimates of the 1 to 59–month diarrhea mortality proportion of 15.6% in Niger and 14.8% in sub–Saharan Africa [37], while the EAVA value of 25.8% is above these estimates.

An unexpected finding, at least on initial examination, both for EAVA and PCVA, was the low proportion of neonatal deaths caused by preterm delivery, respectively, 2.6% and 2.2%. Even including all preterm comorbidity, the EAVA and PCVA levels were, respectively, 9.1% and 7.1%. This compares to CHERG's 2013 modeled estimates of 31.3% of neonatal deaths in Niger and 30.5% in sub–Saharan Africa [37].

Possible reasons for the large differences between the current findings and the modeled estimates include: 1) falsely low reporting of short pregnancy duration by the current study subjects (both the EAVA algorithm and PCVA minimum criteria required pregnancy duration of less than 8 months or less than 9 months plus symptoms of respiratory distress syndrome), 2) placement of preterm delivery at the bottom of the EAVA hierarchy, whereas the CHERG practice has been to accept the published causes of VA study input data (some of which may have used hierarchies with preterm placed higher up to select among multiple causes) except when more than one underlying cause was given and then to use a hierarchy with preterm delivery above all causes other than congenital abnormalities and neonatal tetanus [38], and 3) acceptance by the CHERG model of less rigorous diagnostic criteria or case definitions, such as 'prematurity', without documentation of pregnancy duration or birth weight [38].

The impact of differently arranged hierarchies to select the main cause of death from among multiple possible causes can be illustrated by comparing the current study's EAVA preterm mortality proportion to the levels in the west African subset of the CHERG model's VA input data. The model for the causes of neonatal death in high mortality countries with poor quality vital registration data, such as Niger, is based on regression of national level covariates data on the relationship between the same covariates and the cause–specific mortality findings of 112 verbal autopsy studies from throughout the world. Nine of these studies are from west African countries, with the proportion of neonatal deaths caused by preterm delivery ranging from 7.3% to 40.6%, and a mean value of 20.8% [39]. If preterm delivery were placed near the top of the current study's EAVA hierarchy, then its level (8.8%) would fall on the low end of these other studies' findings, and so does not appear so "unexpected" as at first glance. Thatte el al's reanalysis of data on the causes of neonatal death in India illustrates the same point. The original study, with preterm delivery near the top of the neonatal causes of death hierarchy, found that 26.9% of neonatal deaths were caused by preterm delivery [33], while moving preterm to the bottom of the hierarchy decreased its mortality proportion to 9% [31].

Another example can be given of the CHERG model estimates for preterm delivery as a cause of neonatal death ap-

pearing to be excessively high when compared to direct measures, but in this case not from a difference in the hierarchies used. The CHERG model estimate for the preterm neonatal mortality proportion in Bangladesh from 2000 to 2013 ranged from 26.1% to 31.2% [37]. The 112 VA studies providing input data to the model included thirteen studies from Bangladesh, with preterm mortality proportion ranging from 0% to 57.2%, median of 18.6% and even the third quartile value, at 24.1%, below the modeled estimate [39]. This example illustrates a question that must be answered through further inquiry and direct, large–scale measures of the causes of neonatal and child mortality in countries with incomplete vital registration data.

Limitations of our study included, first, the well–documented limitations in the validity of all verbal autopsy diagnoses. Much work is ongoing to determine which VA analysis method or combination of methods provides the most valid and reliable diagnoses, but in the meantime VA has proven to be the best source of population–based cause of death data in settings with incomplete vital registration. A second limitation of our study was the long recall period of up to five years that was due to our identifying deaths and conducting VA interviews in the context of a retrospective survey and the need to include a sufficient sample size of deaths. Adequate recall of illness signs and symptoms to determine the population distribution of the causes of children's deaths for up to 18 months after death has been documented [40]; still, the effects of diminishing memory with time may have compromised the validity of our findings. This same potential limitation will invariably be present with large–scale VA studies taking a retrospective survey approach, so research to examine the actual effect of such a lengthy recall period is warranted.

In summary, we conducted a national level verbal autopsy study to provide direct estimates of the causes of neonatal and child deaths in Niger. These data can be used on their own to supplement modeled estimates of cause–specific mortality; as well as incorporated into modeling exercises to improve modeled mortality estimates. Further studies are warranted to examine whether direct measures from well–conducted nationally–representative verbal autopsy assessments or modeled estimates of the causes of death are to be preferred. This was not a validation study and so could not definitively determine which analytic method, EAVA or PCVA, provided the most accurate estimates of the cause proportions of mortality. However, the plausibility of the diagnosis of early onset neonatal infection, established through its close association with maternal infection, and the ecological plausibility check of the diagnosis of child meningitis, suggest that at least for these two diagnoses the EAVA method is to be preferred. Validation studies are needed to fully assess this method's validity and to compare the method to the newer statistical approaches to VA analysis, a comparison which has yet to be performed.

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PAPERS

Social autopsy of neonatal mortality suggests needed improvements in maternal and neonatal interventions in Balaka and Salima districts of Malawi

Alain K. Koffi[1], Tiope Mleme[2],
Humphreys Nsona[3], Benjamin Banda[4],
Agbessi Amouzou[5], Henry D. Kalter[1]

[1] Department of International Health, Johns Hopkins
   School of Hygiene and Public Health, Baltimore,
   MD, USA
[2] National Statistics Office, Zomba, Malawi
[3] Ministry of Health, Blantyre, Malawi
[4] National Statistics Office, Lilongwe, Malawi
[5] UNICEF, New York, NY, USA

Background The Every Newborn Action Plan calls for reducing the neonatal mortality rates to fewer than 10 deaths per 1000 live births in all countries by 2035. The current study aims to increase our understanding of the social and modifiable factors that can be addressed or reinforced to improve and accelerate the decline in neonatal mortality in Malawi.

Methods The data come from the 2013 Verbal and Social Autopsy (VASA) study that collected data in order to describe the biological causes and the social determinants of deaths of children under 5 years of age in Balaka and Salima districts of Malawi. This paper analyses the social autopsy data of the neonatal deaths and presents results of a review of the coverage of key interventions along the continuum of normal maternal and newborn care and the description of breakdowns in the care provided for neonatal illnesses within the Pathway to Survival framework.

Results A total of 320 neonatal deaths were confirmed from the VASA survey. While one antenatal care (ANC) visit was high at 94%, the recommended four ANC visits was much lower at 41% and just 17% of the mothers had their urines tested during the pregnancy. 173 (54%) mothers of the deceased newborns had at least one labor/delivery complication that began at home. The caregivers of 65% (n = 75) of the 180 newborns that were born at home or born and left a health facility alive perceived them to be severely ill at the onset of their illness, yet only 44% (n = 80) attempted and 36% (n = 65) could reach the first health provider after an average of 91 minutes travel time. Distance, lack of transport and cost emerged as the most important constraints to formal care–seeking during delivery and during the newborn fatal illness.

Conclusions This study suggests that maternal and neonatal health organizations and the local government of Malawi should increase the demand for key maternal and child health interventions, including the recommended 4 ANC visits, and ensure urine screening for all pregnant women. Early recognition and referrals of women with obstetric complications and interventions to promote maternal recognition of neonatal illnesses and care–seeking before the child becomes severely ill are also needed to improve newborn survival in Balaka and Salima districts of Malawi.

Correspondence to:

Alain K. Koffi
Department of International Health
Johns Hopkins Bloomberg School of Public
Health
615 N. Wolfe St., Room E8610
Baltimore, MD, 21205, USA
akoffi1@jhu.edu

The international community has recently published the Every Newborn Action Plan, endorsed by governments, the private sector, civil society and other stakeholders, that calls for reducing neonatal mortality rates in all countries to fewer than 10 deaths per 1000 live births by 2035 [1]. This new plan postulates that high coverage of interventions before, during and after pregnancy could save nearly 3 million women, stillbirths and newborns by 2025 in 75 high–burden countries [1].

With 68 deaths per 1000 live births in 2013, Malawi is one of the 60 countries that has had a remarkable decline in under–five mortality by at least 72% since 1990, and is among the top 10 countries with the largest declines in neonatal mortality: from 50 to 23 neonatal deaths per 1000 live births in 1990 and 2013, respectively [2]. Nevertheless, much needs to be done to achieve more. Further reductions in neonatal deaths at the country level in particular will also require better knowledge of direct causes, but also the determinants that lead to these deaths.

More recently, there has been a growing interest in the use of a social autopsy tool to explore the social, behavioral, and health system determinants of maternal, newborn, and young child deaths [3,4].

Previous research on the topic suggested that the determinants of neonatal death may be socio–environmental, behavioral or related to quality of health care [5]. Santarelli [6] explained that countries could produce the desired neonatal health outcomes if the capacities and awareness of individuals, families, and communities – in other words, the social determinants of health – are improved, and linkages between them and the health care delivery system are built and strengthened. Similarly, current international opinion suggests that both facility and community approaches are important to ensure the continuum of care throughout pregnancy, childbirth, and postpartum periods [7,8]. In addition, reviews concluded that effective interventions for maternal and neonatal health already exist, and that large reductions in mortality could be achieved by increasing their coverage [9,10].

The overall objective of this study focused solely on the social autopsy component of the data to uncover the most common household, community and health system factors that contributed to the newborns' deaths. Specifically, the study aimed to: 1) review the coverage among deceased neonates of key and evidence–based interventions along the continuum of normal maternal and newborn care, ie, interventions that should be normally accessible to all pregnant mothers and newborns; and 2) describe breakdowns in the care provided for neonatal fatal illnesses within the Pathway to Survival framework. This information is intended to increase our understanding of the social and

modifiable factors that can be addressed or reinforced to improve the design and implementation of maternal, neonatal and child health programs in Malawi.

METHODS

Study sites/districts and sample

The VASA interviews in Malawi were conducted regarding deaths identified by a 24 000–household survey for the Real–time Mortality Monitoring (RMM) project undertaken by the National Statistics Office and Johns Hopkins Bloomberg School of Public Health (JHU) from October 2011 to February 2012 in the districts of Balaka and Salima, in the South and Central Regions of Malawi, respectively. The survey used a full birth history interview of women 15–49 years of age to measure child mortality. Details of the RMM survey procedures are published elsewhere [11]. To limit issues related to faulty recall, while obtaining an adequate sample size, the VASA study examined deaths within a 4–year recall period. There were 537 neonatal (0–27 days of age) deaths and 1018 deaths of young children (1–59 months of age) from 2008 to 2011. In order to decrease the respondent's burden, we selected one death per household and that procedure resulted in a sample size of 476 neonatal deaths and 819 1–59 month–old deaths (total: 1295 deaths), which provided a precision of ±7% for neonatal deaths and ±5% for young child deaths. The current paper reports on the findings for the neonatal deaths.

Data collection tools and VASA interview

A detailed description of the tools is available in a recent study [12]. In summary, the original English version of the VASA questionnaire was translated into the Malawi local language, Chichewa, which is spoken by most persons in the study area. A local anthropologist was recruited to do the translation and another team of two experienced staff members at the Malawi National Statistical Office (NSO) independently back–translated the Chichewa questionnaire and compared this to the original English questionnaire. The discrepancies were then scrutinized to determine the source of the errors and these were corrected through consultations between the anthropologist and the back translators. Finally, the translations were inserted into a CSPro–based software application developed to enable the direct, field–based CAPI (Computer Assisted Personal Interview) capture of the VASA interview data on a netbook computer.

Data collectors were recruited based on prior experience in conducting structured interview mortality surveys, in utilizing a personal or netbook computer or Personal Digital Assistant (PDA) and any other experience in the use of electronic devices, such as smart phones for data collection.

The study preferred female data collectors due to the cultural aspects of the setting, and to a lesser extent religious beliefs in the study areas, where topics related to pregnancy, caregiving, still births and child deaths are most openly discussed among the women. Data–collectors received a three–week training session.

The training focused on technical aspects as well as ethical issues in matters of sensitivity, confidentiality, and prescribed assistance to bereaved respondents. It also included three day–long visits to the field for practice during which the fieldworkers familiarized themselves with the questionnaire and the use of netbook computers in conducting interviews.

In each district, four teams of four interviewers and one supervisor were constituted for the fieldwork and two field coordinators were also recruited to conduct additional quality control of data collected and liaise the fieldwork to the study headquarters at NSO.

The interviewers were trained to select as the respondent the person most knowledgeable of the child's fatal illness and care provided to the child for the illness. The interview covered the fatal illness from onset to death, including for neonatal deaths, the mother's pregnancy and delivery. Hence, additional eligible respondents were permitted if necessary. In cases with discordant responses among respondents, the main respondent's answers outweighed that of the others.

Most of the fieldwork was conducted from March 8 to April 26, 2013. The CAPI capture allows for automated implementation of skip patterns and internal consistency checks that considerably improve the quality of the interview being conducted. However, further review of the collected data revealed 172 cases with large discrepancies between the expected (from the RMM survey) and observed birth dates, ages at death and/or gender of the deceased children. Thus revisit of those households was conduct in order to resolve the discrepant cases, along with some missed and postponed interviews.

Data analysis

The analysis of data on preventive and curative care followed the same procedures as described in a prior publication [12]. In summary, the analysis was guided by the coverage of key indicators along the continuum of normal newborn care for well children and illness recognition and care seeking for child illnesses encompassed by the Pathway to Survival model [13–15]. The study added an extended pathway for neonatal illnesses that examined the continuum of normal antenatal care and recognition of and care–seeking for maternal complications during pregnancy, labor and delivery. In order to assess the impact of perceived illness severity on caregivers' attempts at care–seeking for their child's illness, a scoring system was developed based on their reports of the child's feeding behavior, activity level and mental status. Details of the method were provided in a prior paper [12].

Cronbach's alpha coefficients [16] of the summated scores showed values of 0.93, 0.95 and 0.96 at onset of the fatal illness, when the decision to seek care was made, and after leaving the health provider, respectively. This suggested that the items in the scores elicited highly consistent responses, justifying the reliability of the summated scores according to Nunnaly criterion [17].

Ethical considerations

Ethical clearance for the VASA study was obtained from the Johns Hopkins School of Public Health's Institutional Review Board and the Malawi National Health and Science Research Committee. All respondents provided informed consent before the interview was conducted.

RESULTS

The VASA study completed interviews of 399 (84%) of 476 neonatal deaths identified by the RMM survey within the 4–year recall period and selected for study by the VASA. Of these, 290 were confirmed as neonatal deaths; 34 and 75 were determined to be young child deaths and stillbirths, respectively. Inversely, the VASA interview found that 30 of the initially sampled young child deaths were neonatal deaths. In total, the VASA study in Malawi completed 320 neonatal deaths interviews that are included in the present study.

Demographic and household characteristics

The demographic characteristics of the deceased newborns are presented in **Table 1**. The median age at illness onset was 1 day (Mean: 3.7, standard deviation (SD): 5.70). The illness of half of the newborns lasted less than a day (Median: 0 days). Seventy percent of the deaths occurred within the first week after birth. Neonatal death was more prevalent among boys than girls with a masculinity ratio of 131. The majority of births (69%) occurred at a health facility. Similarly, 59% of the newborns died at a health facility or on– route to a health facility. Of the 219 neonates born at a health facility, about 62% died at that facility, ie, they did not leave alive.

The characteristics of the mother, her domestic partner, and the household are shown in **Table 2**. Approximately 84% of the mothers were married or living with a man at the time of the interview, the vast majority of them (73.8%) entered in union before 20 years of age. In the survey, the

Table1. Characteristics of the deceased neonates

CHARACTERISTICS	FREQUENCY (%)
Sex:	
Boy	181 (56.7%)
Girl	139 (43.3%)
Masculinity ratio (Boy/Girl×100)	131
Mean age at death (in days)	5.1 (median 2; range: 0–27)
0–6	224 (70.0%)
7–27	96 (30.0%)
Median age at illness onset	1 (mean = 3.7; SD = 5.70)
Median illness duration	0 (Mean = 1.6; SD = 2.93)
Place of birth:	
Hospital	122 (38.3%)
Other health provider or facility	97 (30.2%)
On route to a health provider or facility	8 (2.6%)
Home	77 (24.0%)
Other	16 (5.0%)
Place of death:	
Hospital	121 (37.9%)
Other health provider or facility	55 (17.1%)
On route to a health provider or facility	18 (4.3%)
Home	118 (36.8%)
Other	13 (3.9%)
Child was born and died at health facility (without leaving health facility) (n = 219)	135 (61.6%)

SD – standard deviation

Table 2. Characteristics of the mother and her household

MATERNAL CHARACTERISTICS	FREQUENCY (%)
Married or living with a man	268 (83.8%)
Age when first married (years)	18.2 (median 18; range: 12–26)
<16	22 (8.1%)
16–19	176 (65.7%)
20+	64 (23.7%)
Don't know	7 (2.5%)
Mother's mean age at time of child death (in years):	25.7 (median 24; range: 15–47)
<16	7 (2.1%)
16–19	52 (16.2%)
20–24	104 (32.4%)
25+	150 (47.0%)
Don't know	8 (2.3%)
Median years of maternal schooling (in years):	4.0 (mean 4.5; range: 0–14)
0–3	139 (43.5%)
4–6	89 (28.0%)
>6	90 (28.4%)
Don't know	1 (0.2%)
Father years of schooling (mean years of schooling):	6.3 (median 6; range: 0–19)
0–3	67 (24.2%)
4–6	72 (26.0%)
>6	138 (49.8%)
Household characteristics:	
Main breadwinner	
Father	287 (89.6%)
Mother	15 (4.8%)
Other	18 (5.6%)
Main breadwinner is farmer/agricultural worker	115 (35.8%)
Average time at current residence	13.0 (median 10; range: 0–60)
Household size (mean):	4.4 (median:4; range: 1–9)
Household has electricity	11 (3.3%)
Use of piped water –In–house water supply	42 (13.2%)
Use of improved sanitation (Improved pit for toilet)	24 (7.6%)
Separate room for cooking	194 (60.5%)
Household uses firewood for cooking	286 (89.5%)
Floor of the house made of cement	29 (9.0%)
Mean travel time to nearest health facility (minutes)	106 (median: 90; range: 0–420)
Social capital:	
In last 3 y, community worked together on at least 1 of the following: schools, health, jobs, credit, roads, public transport, water, sanitation, agriculture, justice, security, mosque/church	318 (99.4%)
Mother was NOT able to turn to any persons or community groups or organizations for help during the pregnancy or child's fatal illness	102 (31.8%)
Mother and her family have never been denied any of the following community	312 (97.4%)

majority of the mothers of the deceased newborns had little or no education. On average, the mother had 4.5 years of schooling ranging from 0 to 14 years. Hence, about a quarter (24.2%) of the mothers of the deceased newborns were illiterate or had 0–3 years of schooling. The occupation most cited for the breadwinner was farmer/agricultural worker (35.8%).

The average household size was 4.4 persons. Only 3% of the households had electricity, 13.2% had access to an improved source of drinking water, 7.6% used improved sanitation (flush or improved pit toilet), 89.5% of the households used firewood for cooking. About 9% of the households had cement flooring, and 2 in 3 (60.5%) of households had a separate room for cooking. It took 106 minutes on average for the caregiver to reach the usual health center from her household. The families had been living in the same community for about 13 years on average, yet 32% of the mothers did not have anyone to help them during their pregnancy or child's illness.

Maternal and newborn care

The components of the antenatal care (ANC) received by the 93.5% (n = 299) of mothers who completed at least one visit during their pregnancy are shown in **Figure 1**. A quality gap existed because some did not receive all of the ANC components, including blood pressure measurement, urine and blood sample tests, and counseling on proper nutri-

tion and pregnancy danger signs. In the current study, urine testing was very low (17%) among mothers of deceased newborns, and the numbers did not improve (18%) even after four or more ANC visits. Overall, just 14% of the mothers who went to a health provider for at least one ANC visit received ANC of "quality". And the quality gap or
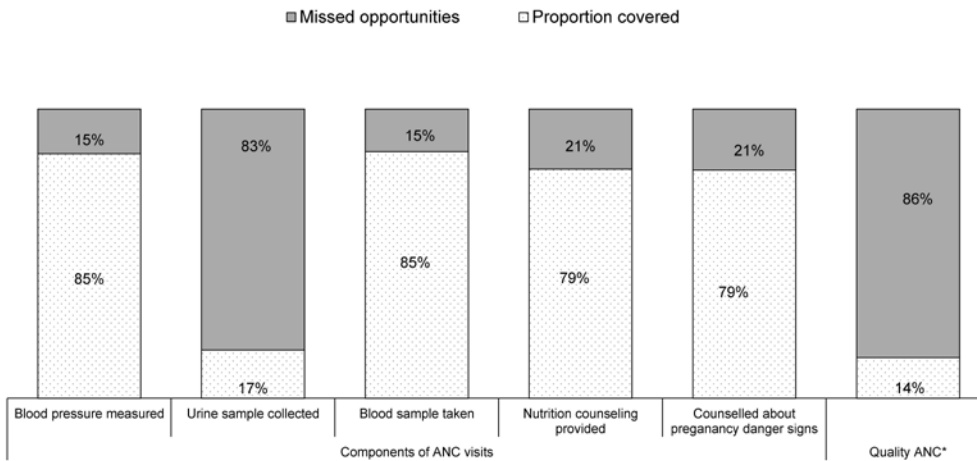
Figure 1. Quality gap for at least one antenatal care visit (n = 299). For women who went to at least one antenatal care (ANC) (n = 299) visit, a quality gap (or missed opportunity) exists and represents the difference between the expected maximum coverage and the actual coverage proportion. Asterisk indicates that quality ANC includes blood pressure checked, urine and blood tested, counseled about nutrition, and counseled about pregnancy danger signs.

missed opportunity ranged from 15% for blood pressure checked to 83% for urine testing.

Figure 2 shows the preventive care received by mothers and newborns along the continuum of care. Just 41% (n = 133) of the mothers had the recommended four or more ANC visits, of which only 15% (n = 19) received ANC of "quality". Two–thirds (68%) of the mothers delivered at a health facility, and an equal proportion were delivered by a skilled birth attendant (ie, doctors, nurses, or midwives). Among the neonates who survived the first day of life, 46% received appropriate thermal care consisting of immediate warming, drying and wiping, wrapping in a blanket, skin–to–skin contact with the mother or being placed in an incubator, plus bathing delayed for more than 24 hours after birth. Only one in three (33%) of the deceased newborns was breastfed immediately (within an hour) after birth. Overall, 67% of the newborns were first put to their moth-

er's breast within 24 hours. About 50% of the newborns were provided hygienic cord care, which includes using a razor blade that is new, boiled or from the delivery kit for cutting the cord, a cord clamp or thread that is new, boiled, or from the delivery kit for tying the cord and either nothing or alcohol or another antiseptic or antibiotic ointment, cream or powder being applied to the cut cord stump.

The maternal complications and care–seeking for these during the pregnancy and/or delivery are presented in **Figure 3**. Of the 320 mothers of deceased newborns, 94 (29%) reported they had one or more pregnancy complication(s) during the last three months, mainly maternal sepsis (n = 36, or 11%) and antepartum hemorrhage (n = 35, or 11%). More than half (n = 173, or 54%) of the mothers had at least one labor/delivery complication that began at home, including preterm delivery (n = 104, or 33%), intra–partum hemorrhage (n = 98, or 30%), and prolonged labor (n = 59,
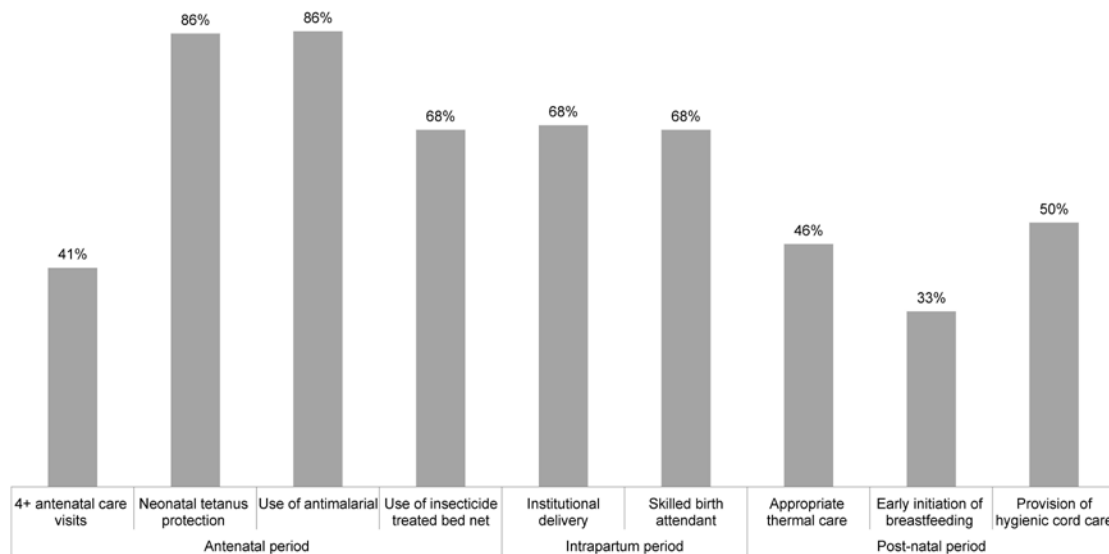
Figure 2. Preventive care of the mothers and newborns (n = 320).
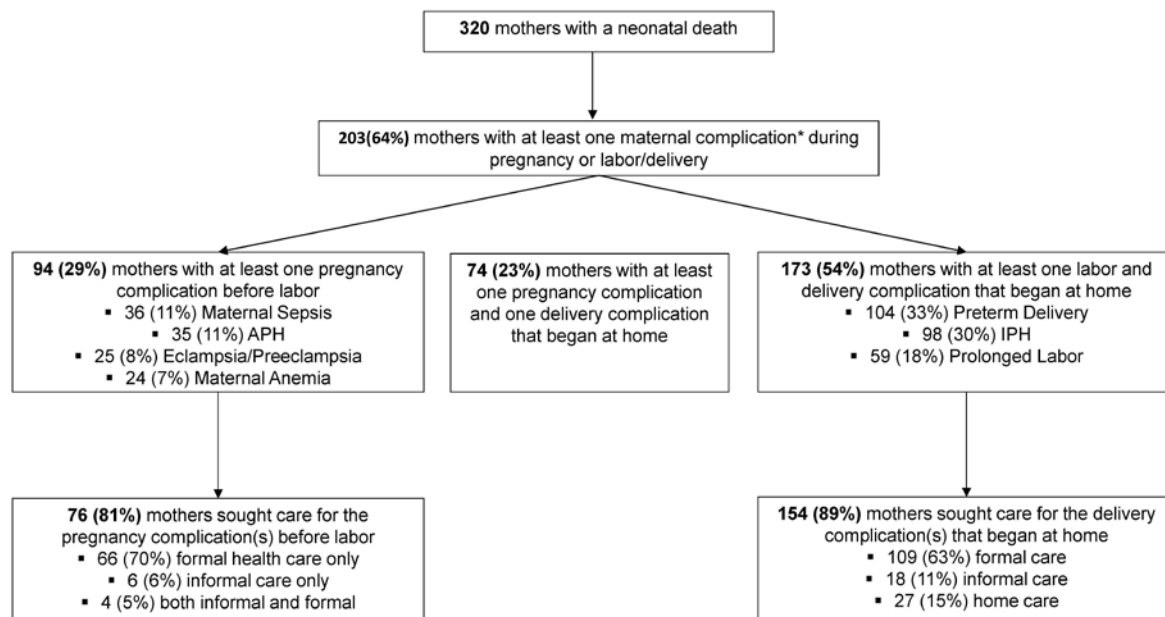
Figure 3. Maternal complications and care-seeking during the pregnancy and delivery (n = 320). Asterisk indicates the following: Maternal complications – Maternal sepsis = Fever+(Severe abdominal pain OR Smelly vaginal discharge); Eclampsia/ Pre-eclampsia = Severe headache+(Blurred vision OR Puffy face OR Convulsions OR High blood pressure); Maternal anemia = Severe anemia or pallor and shortness of breath+(Too weak to get out of bed OR Fast or difficult breathing); Ante–partum hemorrhage (APH) = Any bleeding before labor; Intra-partum hemorrhage (IPH) = Excessive bleeding during labor or delivery.

or 18%). Overall, 75% (n = 70) of the 94 mothers with a pregnancy complication sought some formal care for the complication. Several (n = 109, 63%) of the 173 mothers with at least one labor or delivery complication that began at home sought some formal care.

Care–seeking for newborn's fatal illness

The breakdowns in the Pathway to Survival that contributed to the newborn deaths are presented in **Figure 4** for the 180 newborns who were either born at home or left the delivery facility alive and had information on care–seeking. Another 135 of the 320 newborns were born and died at the health facility without leaving, and five others had an illness that began at the facility where they were born and died later at home, but data these cases had no information on care–seeking.

When the 180 newborns' fatal illnesses began, 97.8% of care–takers could recognize and report a severe or possibly severe symptom. Yet, the mothers of only 110 (61.1%) of the newborns sought or tried to seek care; 37 (20.6%) of the newborns "died immediately" and no care was given or sought for the other 33 (18.3%) newborns. And, 73% and 38%, respectively, of the neonates in the last two groups were ranked as being severely ill at the time their caregivers first noticed the illness. Understandably, for the group

that died "immediately," both the median age at illness onset and the median illness duration were 0 days, meaning the newborns were born and died quickly (or "immediately") on the day of birth. For the "no care given or sought" group, the illness occurred on the third day of life (day 2) and lasted 0 days as well.

Regarding the group of the mothers of the 110 neonates who received, sought, or tried to seek care, the vast majority (79%, n = 87) first sought care outside the home, 23 first received care inside the home, and 4 of these 23 later sought or tried to seek outside care. A total of 91 sought, or tried to seek care outside the home, and the median length (or delay) from illness onset until formal health care seeking was 1 day.

Among those who sought outside care, the majority (83.5%, or n = 76) sought formal care only, 4 sought both informal and formal care, and 11 informal care only. The delay to seeking formal care was 1 day, both for those who sought informal and formal care and those who sought only formal care.

Out of the 80 newborns for whom formal care was sought, 31 (38.8%) were already severely ill at the time the caregiver decided to seek care. Fifteen (or 18.8%) did not reach the health facility because they died before setting out, died on–route or could not reach the health provider. The re-

maining 65 (81.3%) newborns could reach the first health provider, on average, after 91 minutes travel time. More than two–thirds (n = 46, 70.8%) of these 65 newborns were taken to an NGO or government clinic or facility led by Health Surveillance Assistants (hereafter referred to as a "first level facility)," and the other 19 (29.2%) were taken to a non–governmental organization (NGO) or a government hospital.

Twenty–six (40%) of the 65 neonates that reached a first provider died at that provider, including the 13 out of 19 (68%) that reached a hospital. Yet, 14 of the 39 (36%) who left the first health provider alive were not referred nor received any home care recommendations. However, when recommendations were received, or referral provided, most of the caregivers (80–100%) followed all the recommendations or accepted the referral and went to a second health care provider.

Maternal and newborn care–seeking constraining factors

The care–seeking constraints for the delivery and for treatment of the neonatal illness are described in **Figure 5**. In total, 118 mothers reported concerns or problems regarding delivering at a health facility, of which 53 succeeded in doing so. In other words, of the 219 mothers who delivered at a health facility, 53 (24.1%) had to overcome some concerns or constraints to deliver at the facility. Conversely, the vast majority (64%, n = 65) of the 101 mothers who did not deliver at a health facility reported constraints or concerns in doing so. And the difference between the two proportions (24.1% vs 64% was statistically significant (P < 0.001).

Of the 143 neonates that sought/tried to seek care or not (ie, the groups of 33 "no care was given or sought" and 110 "received, sought or tried to seek care") for the fatal illness, the proportion of those who reported any constraints was statistically higher in the subgroup that either did not seek care or sought home or informal care only (n = 63) than in the subgroup that sought some formal care (n = 80) (54.1% vs 23.6%, P < 0.001).

Among the care–seeking constraints reported either during delivery or during the newborn fatal illness (**Figure 5**), the following emerged as most important: distance (52–74%), lack of transport (49–68%), and cost (21–74%).

DISCUSSION

The objective of this social autopsy study was to shed light on the social, behavioral, and health system determinants of newborn deaths from 2008 to 2011 in Balaka and Salima districts in Malawi.
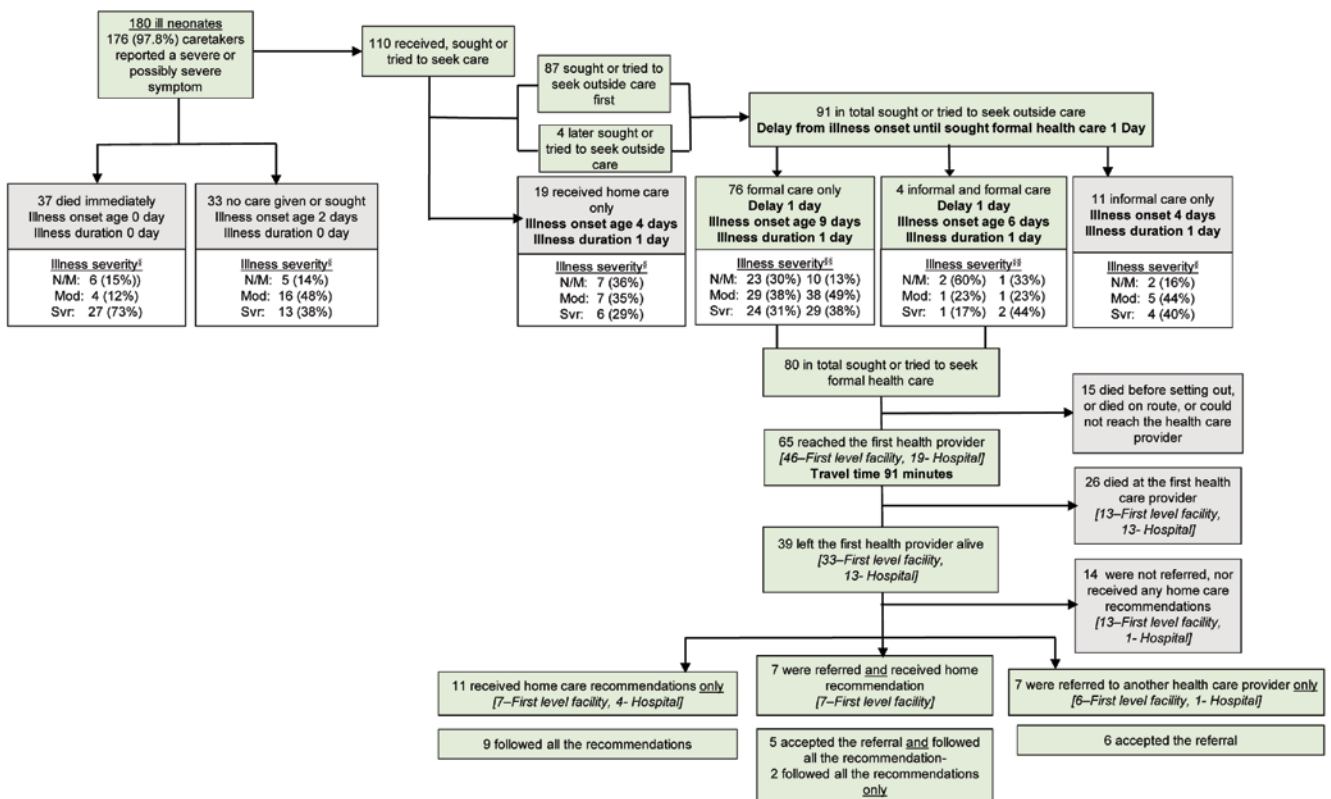
Figure 4. The "Pathway to Survival" for 180 neonatal deaths (born at home or left the delivery facility alive), Malawi 2008-2011. Notes: §Illness severity at onset; §§Illness severity at onset and when caregiver decided to seek formal care; N/M – normal/mild, Mod – moderate, Svr – severe.
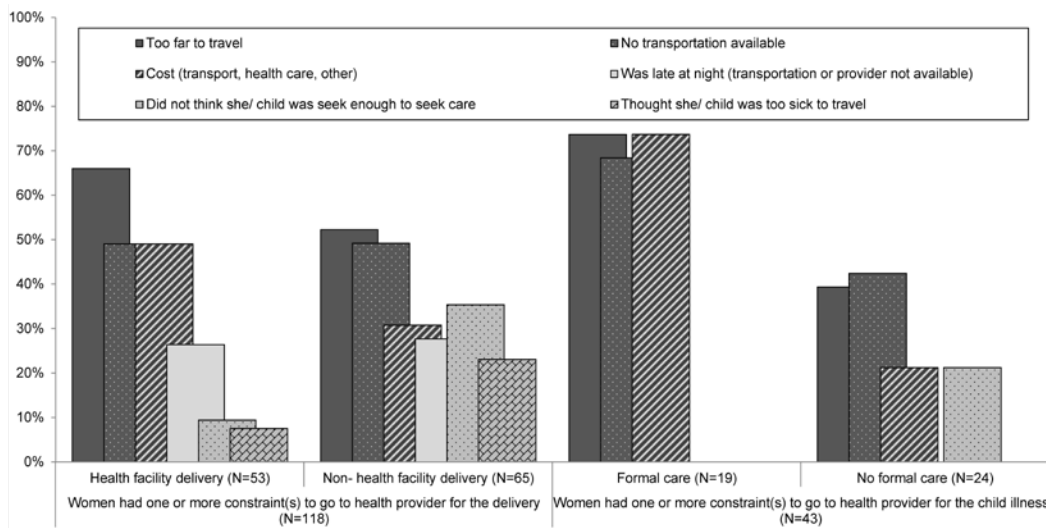
Figure 5. Main care–seeking constraints for the delivery and for the neonatal illness.

Demographic and household characteristics

Our study showed that the majority of the deceased newborns were from households with poor socioeconomic conditions, lacking basic commodities such as electricity, water sanitation and clean water. The households were crowded and about 90% used firewood for cooking. The breadwinners were mostly farmers. These hardship living conditions have been shown to increase the risk of illness for mothers and newborns because they face more challenges in accessing timely, high–quality care compared to wealthier families [18].

The gender differential in neonatal mortality is also worth mentioning. It is well known that more boys than girls are born globally, but boys are more likely to die than girls in the neonatal period mainly due to higher vulnerability to infectious diseases [19]. Likewise, in this study, the number of newborn deaths was 1.3 times greater among male than female children.

Maternal complications and care during pregnancy, labor and delivery

Recent reports from Malawi have shown improvement in perinatal and neonatal outcomes and an increased coverage by health services and skilled birth attendants across the country [2,20]. Our study found that for mothers with a neonatal death, coverage of at least one antenatal visit was relatively high at 94% in these two Malawi districts. Yet coverage of the recommended minimum four visits (41%) was much lower. It is well known that certain interventions such as iron and folic acid, antimalarial drugs prophylaxis, syphilis testing and treatment, and tetanus toxoid immunization cannot be effectively delivered with only one antenatal visit. Thus, if antenatal care is to contribute to reducing the

neonatal mortality rate in the study setting, a minimum of four antenatal care visits with the full range of evidence–based interventions at each visit is required [21].

The quality gap found in our study implies that 86% of mothers with a neonatal death did not receive the quality of antenatal care that they needed—even when they had contact with the health system during their pregnancy. This quality gap persisted even with an increased number of ANC visits. Without improved quality, increased antenatal coverage is unlikely to substantially improve perinatal and neonatal outcomes [22,23]. For instance, during the antenatal visit(s) the vast majority of mothers did not have their urine tested during the course of their pregnancy. Similarly, according to a 2010 emergency obstetric and newborn care (EmONC) facility–based survey [24] and the most recent Malawi Service Provision Assessment [25], very few facilities offering ANC services in the country have the capacity to conduct laboratory diagnostic tests due to lack of equipment, including urine chemistry testing. And Government facilities were least likely to have dip sticks for urine protein and glucose (12% and 9%, respectively) compared to facilities managed by other authorities [25]. This appears to be a problematic situation. A urine test should be conducted during the first prenatal exam and then at least periodically in future prenatal visits. Urinalysis is used to assess bladder or kidney infections, diabetes, dehydration, and preeclampsia by screening for high levels of sugar, protein, ketones, and bacteria [26, 27]. Higher levels of protein may suggest a possible urinary tract infection (UTI), or kidney disease. It is well established that during pregnancy, UTI is associated with increased risks of preterm delivery, even when the infection is asymptomatic [28]. The present study found that preterm delivery was the main complication experienced by the mothers during delivery, which coincides with that of "Born Too Soon" reports in

which Malawi has the highest rate of preterm birth in the world [29].

The dearth of available information on UTI rates in Malawi [28], added to the low proportion of urine testing among mothers as shown by the current study could reflect the overall lack of health care infrastructure for research, screening, and treatment programs in Malawi. A study design that would investigate the prevalence of UTI among women with preterm delivery complications in the country would be of importance since that could fuel policy makers' interest and justify the promotion of universal modern antenatal urine screening, combined with appropriate follow–up management or treatment of UTI, either symptomatic or asymptomatic. Elsewhere [28], screening and treatment of asymptomatic bacteriuria (ASB) has improved preterm birth and low birth weight outcomes in several developed countries and would likely improve maternal and neonatal health worldwide, particularly in developing countries such as Malawi. ASB screening has been thus included in the WHO ANC package. Darmstadt et al. estimated a reduction of prematurity and low birth weight by 20–55% and neonatal mortality due to preterm birth by 5–14% [9].

The fact that the vast majority of women received at least one antenatal care visit offers an opportunity to effectively implement the ASB screening. We acknowledge that one of the main barriers to ASB screening resides in the non–existence of adequate clinical microbiology resources in these settings. Some authors have suggested the need for innovative alternatives such as portable ASB screening devices or the need for simple methods that could be used by community health workers outside traditional clinic settings [28].

The majority (63%) of mothers who experienced intrapartum complications that started at home sought formal care. In addition, the majority of newborns (59%) born at a health facility did not leave the facility alive. These findings suggest that these facility deliveries included high–risk or complicated cases with a higher risk of early neonatal death, a situation that has been observed in other studies [30,31]. The quality of care in the facilities cannot be assessed by this study but must be examined to determine if more of these deaths could have been prevented.

In addition, the majority of mothers whose newborns were born and died in a health facility without leaving had one or more labor or delivery complications that started at home. The vast majority of intrapartum events—such as heavy vaginal bleeding, preterm delivery and prolonged labor—have been described as significant risk factors for early neonatal deaths [32,33]. Therefore, early recognition, immediate care–seeking and referral (when needed) of women with obstetric complications to an appropriate cen-

ter should be an intervention program priority, including essential and emergency obstetric and newborn care and newborn resuscitation services [34].

Care–seeking for newborn's fatal illness

Of the 180 newborns whose fatal illness started at home, almost all the caretakers (97.8%) recognized a severe or possibly severe symptom. Yet only 80 sought or tried to seek formal care, of which the proportion of the perceived severely ill newborns increased from 31% to 39% from onset of the illness to the moment that caregivers decided to seek formal care. Yet just 65 (36%) could reach the first health provider after an average 91–minute travel time. This finding suggests that there was a delay in recognizing an illness of severity that should have led to prompt care–seeking. In addition, caregivers had to overcome the constraining travel distance to reach the health facility. Timing is important for providing neonates with appropriate and prompt care at the onset of illness, and any delays in the decision to seek care, or in taking the action of care–seeking can be fatal to the infant [35]. Yet, prior to the decision to seek care, caregivers need to be able to recognize the illness danger signs of their newborns. This awareness can be particularly challenging in the neonate due to the lack of specific symptoms [36–38]. Care–seeking was also delayed for several neonates who became sick after the first week of life and whose illnesses were less serious at the onset until they became more severely ill. Other studies have described interventions to promote maternal recognition of neonatal illnesses and care–seeking before the child becomes severely ill [39–41].

Our study also suggests that referral and home care recommendations for sick newborns need to be improved at least among first level health facilities, as findings show that more than a third (13 newborns out of 33 that reached and left a first level facility) of the of sick newborns were not referred nor received any home care recommendations.

Care–seeking constraining factors

Our findings further show that distance, lack of transport and unaffordable costs, including transportation and health care costs, emerged as the most important constraints, both for any pregnancy or labor/delivery complications and for newborn fatal illness. The Ministry of Health estimated that only 54% of the population has access to a health facility within a 5 km radius [42]. These barriers suggest that women from the most remote areas are still at a disadvantage because they have the longest distance to travel. They may also deliver on–route to the health facility, where they are arguably worse off than if they had delivered at home. They may only set out when their child's severe illness has already started. Powell et al. [43] described a financing

scheme in Nepal that provided transport costs to further reduce the barriers to health care for the poorest women, but this was challenging to implement. Another example includes the implementation of an obstetric helpline and taxi transport schemes in response to the financial and distance barriers identified by the Maternal and Perinatal Death Inquiry and Response (MAPEDIR) project in Dholpur district of Rajasthan State in India [44].

Limitations

The limitations of this study have been also discussed elsewhere [12].The data could have been affected by recall bias and the possibility of providing socially desirable answers to sensitive questions, given the recall period of about 4 years, in addition to the fact that the respondents were the main caregivers of the deceased child. However, we believe that the conversational and prompting modes used during the face–to–face interviews and the involvement of experienced interviewers may have led to better overall recall of events. In addition, the study was conducted in just two districts in Malawi; hence readers should exercise caution in the attempt to generalize the findings to the entire country situation. A national and representative sample VASA study design could offer a clearer picture of the entire country. The inclusion of a control group would have allowed the analysis to test whether there were significant differences between the coverage of interventions among cases (deceased newborns) and controls (alive newborns); however, the lack of a comparison group in SA studies is common and not so necessary since we were studying interventions that should be accessible to all pregnant mothers and newborns and that had been proven to be effective against neonatal mortality [15].

CONCLUSIONS

Encouragingly, Malawi appears to have made great strides recently in achieving declines, albeit slow, in neonatal mortality rates. The current study went beyond the classic review of interventions for deceased newborns and their mothers along the continuum of care, to identify the breakdowns within the Pathway to Survival that led to newborn deaths and to examine the care–seeking barriers for maternal complications during pregnancy and delivery, and the newborns' fatal illnesses that contributed to the deaths. The ultimate goal of this study was to increase our knowledge of modifiable factors that could be targeted in order to improve neonatal health for progress in an overall more rapid decline in neonatal mortality in Malawi. Hence, our main results confirmed significant progress in some areas of women's and children's health, such as facility delivery and skilled birth attendance and attendance of mothers to at least one antenatal visit. Yet, increasing the number of pregnant women who obtain antenatal urine testing and treatment and who attend at least 4 ANC visits as recommended by WHO could be a worthwhile approach for improving birth outcomes. In addition, early recognition and referral of women with obstetric complications and interventions to promote maternal recognition of neonatal illnesses and care–seeking before the child becomes severely ill are needed to accelerate the decline in neonatal deaths in the study districts.

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