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There are reasons for optimism among children in sub-Saharan Africa. The recent study estimated that the total number of deaths in children younger than 5 years decreased from 9.6 million to 7.6 million per year globally during the past decade, showing a continued progress towards the UN's fourth Millennium Development Goal (MDG4). Moreover, the world's extreme poverty rate (people living below US$ 1.25 a day) recently fell to less than half of its 1990 value, meeting the UN's MDG1. In addition, more than 2 billion people gained access to improved drinking water sources, such as piped supplies and protected wells, between 1990 and 2010, meeting the UN's MDG7 five years before the deadline in 2015.

The photograph is the courtesy of Alasdair Campbell, personal collection

Journal of Global Health: The Mission Statement

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

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

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

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

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

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

March 7, 2011

The Editors, *Journal of Global Health*

EDITORIAL

Addressing global health priorities: Balancing investments in existing and emerging approaches

Igor Rudan, Ana Marušić, Harry Campbell

One of the common themes in contemporary global health is finding an optimal balance between investments in existing and emerging approaches to fight global health priorities. Existing interventions have been proven to be effective, but they usually have limitations. Emerging interventions could potentially bring greater gains at a lower cost, but health gains are usually uncertain and take much more time to achieve. There are no simple solutions on how to balance funding support to these two competing approaches, but some components of successful strategies are becoming increasingly apparent. Transparency over the expected return on investment, style of investment and time horizon can assist rational investment decisions.

One of the common themes in contemporary global health is finding an optimal balance between investments in existing and emerging approaches to fight global health priorities [1]. Existing interventions that have been proven to be effective can be scaled up at a certain cost to provide additional health gains, but they usually have limitations. Supporting the development of novel (emerging) interventions could potentially bring greater gains at a lower cost, but health gains are usually uncertain and take much more time to achieve. There are no simple solutions on how to balance funding support to these two competing approaches in order to achieve greatest gains at the lowest cost within a defined period of time [2]. However, some components of successful strategies are beginning to seem increasingly apparent. As a starting point, we could pose this question: why should anyone choose to invest in either scaling up existing health interventions, or developing new ones? Any investment can typically be linked to an expectation of the investor for some return on the investment. What can be seen as the return on investment in this case? This probably depends on who the investors are. Governments and international agencies are expected to use taxpayer's money to reduce the overall disease burden in a cost-effective way. Industry, however, may be primarily interested in generating patents on discoveries that could secure financial profit from future sales of both existing and emerging interventions. Not-for-profit organizations and private donors may have their own specific priorities that do not necessarily need to be either rational or transparent [3,4]. When balancing investments in existing and emerging health interventions, investors need to carefully consider the style of investing they wish to adopt. Among an incredibly broad set of options, investors can choose to support only one or a subset of them; and can adopt a predominantly risk-neutral, risk-averting or risk-seeking approach. Governments are typically expected to adopt a risk-neutral approach and diversify their support across a set of proven existing interventions, while also identifying a few promising emerging approaches which they would like to introduce in the future. Industry would be more likely to adopt a risk-averting strategy by minimizing support to complex downstream research and focusing on improvements to existing interventions, while carefully selecting the most promising emerging ones that are already in the pipeline for investment. Private donors may adopt a risk-seeking strategy by focusing on a very specific target within a set time frame. They may be in a position to invite the most original ideas and out-of-the-box thinking that could revolutionize global health and eradicate the problem entirely, while accepting the risk that

When the investment context is one of a short time horizon to achieve returns on investment, the balance will be heavily skewed toward support for implementing and upgrading existing interventions. If the investment context is one with a much longer-term horizon, the balance will shift toward more uncertain, higher risk options, which hold the promise of considerably greater benefits per unit of cost.

most of the funding will ultimately fail to result in any progress at all [5]. The time-frame within which investors expect a return on their investment is another critically important factor to consider. When the investment context is one of perceived urgency or of a short time horizon for action to achieve returns on investment, the balance will be heavily skewed toward support for implementing and upgrading existing interventions. If the investment context is one with a much longer-term horizon then the balance will shift toward more uncertain, higher risk options, which hold the promise of considerably greater benefits per unit of cost [6,7]. In this issue, we present several papers that closely relate to these issues. An expert opinion exercise conducted by Bahl et al. focused on setting research priorities to reduce the global burden of preterm birth and low birth weight [8]. Rudan et al. present research priorities among emerging interventions against major childhood infections, as determined by a multidisciplinary panel of international experts [9]. Chopra et al. describe and discuss the complex interplay between the determinants of cost-effectiveness and equity when planning the scale-up of health interventions that can achieve child mortality reduction [10]. Finally, Feng et al. assemble a unique and large data set on a broad range of health and socio-economic variables and then use multivariable approaches in an attempt to understand the relative contributions of a range of recent health and social changes within Chinese society to the dramatic reduction of child mortality which has occurred during the period 1990-2006 [11].

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Africa

In Sierra Leone, traditional birth attendants (TBAs) were banned from assisting deliveries some 18 months ago, when the Sierra Leone government introduced their free health care initiative. Under this initiative, pregnant women receive support so long as they deliver in a clinic or hospital. The pros and cons of TBAs is the subject of fierce debate among health care professionals worldwide. WHO argues that, until there are sufficient midwives, the best policy is to train the TBAs in simple outreach work so that they can monitor low-risk pregnancies while referring more complicated cases to the clinics. (*The Guardian*, 17 Jan 2012)

Medecins Sans Frontieres (MSF) has shut down two major medical centres in the Mogadishu, Somalia, after two of its aid workers were shot dead by a former colleague last month, the international medical aid agency reported in January. (*Reuters*, 19 Jan 2012)

Ivory Coast is abandoning free health care for all after a brief experiment, because the costs escalated rapidly, health minister Mr Yoman N'dri said in Abidjan. From February 2012, the free service will only be available to mothers and their children under six years of age. Aid organisations say the government move is understandable, given the country's recent political turmoil. (*The Guardian*, 27 Jan 2012)

In April this year, The Ghana Health Service became the first African country to simultaneously introduce pneumococcal and rotavirus vaccines in its national immunization programme, in a bid to fight pneumonia and diarrhoeal diseases. The ceremony at which the vaccines were introduced also served as the platform for the official launch of the second African Vaccination Week (AVW), which is being observed from 23 to 28 April. Ghana is receiving backing from the GAVI Alliance. As well as being immunised against rotavirus and pneumococcal disease, children will also continue to be vaccinated against polio and yellow fever, as well as receiving the pentavalent vaccine (five in one) which protects against diphtheria, tetanus, whooping cough, hepatitis B and *Haemophilus influenza* type b. (*Ghana News Agency*, 26 Apr 2012)

African economic growth in the past decade, averaging around 5% on the continent, is certainly good news compared with two decades of increasing poverty. But the reason for that growth is mainly the large-scale export of commodities, with no clear industrial or institutional benefits. "Jobless growth", the source of the uprisings in north Africa, is the norm in Africa; although manufacturing exports quadrupled to over US$ 100 billion in the last decade, manufacturing is actually declining as a proportion of GDP from a fairly stable 17% (between 1965 and 1990) to 13% today. (*The Guardian*, 26 Apr 2012).

Asia

After years of decline, with only 25 polio cases reported in Afghanistan in 2010, last year the number tripled to 76, according to the Afghan Ministry of Public Health. While the total remains small, polio is highly contagious and each detected case is likely an indicator of hundreds of 'silent' ones in children with mild infections, who become carriers. Health workers are alarmed at the reversal of trend, particularly since some of the cases erupted far outside the disease's traditional areas in Afghanistan. (*New York Times,* 16 Jan 2012)

Vietnam has asked international health experts to help investigate a mystery illness that has killed 19 people and sickened 171 others in an impoverished district in central Vietnam. The affected were mostly children and young people. The disease begins with a high fever, loss of appetite and a rash that covers the hands and feet, and it responds well to treatment if detected early, but re-infections are common. The disease was first detected in April 2011, but diminished by October last year, with a fresh epidemics wave starting in March 2012. (*Associated Press*, 20 Mar 2012)

Indonesia is now the world's fifth pentavalent vaccine producer, after the state pharmaceutical firm PT Bio Farma has successfully developed it to meet domestic and foreign needs. The company would also sell the vaccine abroad after securing a certificate from the World Health Organization (WHO), while an estimated 4.8 million infants in Indonesia would receive this vaccine. (*Antara News,* 24 Mar 2012)

The Pakistani medical official who ran a fake CIA vaccination programme to help find Osama bin Laden has been jailed for 33 years. Dr Shakil Afridi may now face decades in jail, despite calls from senior US officials to release the man who helped to track down the al-Qaida chief. (*The Guardian*, 23 May 2012)

Japan's Senior Vice Minister of Finance, Yukihisa Fujita, announced at the African Development Bank's (AfDB) Annual Meetings in June 2012 that the Japanese government intends to provide another US$ 1 billion over the next five years for a second phase of the Enhanced Private Sector Assistance (EPSA) for Africa Initiative, as a follow-up to the G8 Camp David Summit which took place from 18-19 May 2012. (*AfDB*, 02 Jun 2012).

Australia and Western Pacific

The World Health Organization warned that the battle against the age-old scourge of leprosy is not yet over, with more than 5000 new cases reported yearly in the Western Pacific, where the disease was declared eliminated in 1991. (*Washington Post*, 13 Feb 2012)

Australia-based advocate Dr Kate Armstrong voiced her concern in March 2012 that children's needs - let alone their rights – are still being forgotten. In her analysis, the targets now being considered by the World Health Organization and others to reduce the impact of heart disease, cancer and other non-infectious diseases are in danger of being focused solely on adults. Children in the poorest countries die of cancer and asthma and diabetes, but the targets under consideration aim to bring down the deaths of adults over the age of 30. (*The Guardian*, 19 Mar 2012)

Speaking at the Australian National University in Canberra, GAVI CEO Dr Seth Berkley delivered an in-depth speech outlining the crucial role Australian funding will play in saving lives in the developing world over the next decade. He explained that the unique financial structure of GAVI had allowed it to drive a 97% reduction in the cost of the pneumococcal vaccine, driving strong outcomes in the world's 73 poorest nations. Dr Berkley also touched on the need to drive access to HPV vaccine, created by Australian scientist, Professor Ian Frazer. (*GAVI Alliance*, 21 March 2012)

Australia has released a review set to inform the country's future funding and engagement with multilateral organizations and development banks. The Australian Multilateral Assessment measures the effectiveness of Australia's key multilateral partners against a number of components, such as alignment with Australia's aid priorities and interests, cost and value consciousness, and transparency and accountability. (*Devex*, 02 Apr 2012)

Australian researchers are preparing to expand trials for malaria vaccines as drug-resistant strains emerge in developing countries. Swiss non-profit Medecins for Malaria has given A$ 500 000 to the Queensland Institute of Medical Research (QIMR) to expand its trials of malaria vaccines. (*Australian Associated Press*, 26 Apr 2012)

China

The Chinese drug artemisinin has been hailed as one of the greatest advances in fighting malaria since the discovery of quinine centuries ago. Artemisinin's discovery is being talked about as a candidate for a Nobel Prize in Medicine. In one of the paradoxes of history, the drug was discovered thanks to Mao Zedong, who was acting to help the North Vietnamese in their jungle war against the Americans, after which it 'disappeared' for 30 years because of China's isolation and the indifference of Western donors, health agencies and drug companies. (*New York Times*, 16 Jan 2012)

According to the newspaper affiliated to China's health ministry, one year on from the World Health Organization (WHO) freeing Chinese vaccine producers to apply for rights to distribute their products globally, none have qualified to do so. At present, only the Henan-based Hualan Biological Bacterin Co. Ltd, and the Chengdu subsidiary of China National Biotec Group have submitted applications for this "WHO license" for their seasonal flu vaccine and Japanese encephalitis vaccine, respectively. They have not yet won approval. China has 36 of the world's 85 vaccine producers, but without the WHO approval the only route for Chinese vaccines to be distributed globally is if they are donated, or if foreign countries are approached individually. (*Xinhua*, 29 Feb 2012)

China hopes to cap the number of people living with HIV/AIDS at 1.2 million by 2015, up from around 780 000 at present, partly by promoting increased condom use. While praising achievements made over the past few years, including improved life expectancy for AIDS patients, the State Council said that China still faced a difficult task to prevent the spread of the disease. (*Reuters*, 29 Feb 2012)

Tracking the prevalence of the diseases of affluence, the World Health Organization (WHO) reported that a quarter

of those 25 or older now have high blood pressure worldwide, and almost one in 10 has worrying levels of glucose in their blood. The WHO's tally of the latest global health statistics for the first time includes a look at blood pressure and glucose levels, two of the risk factors for diabetes and cardiovascular disease. China will likely be the most significant example among the low and middle-income countries expected to develop strategies and health policies to tackle this problem on a large scale. (*Washington Post*, 16 May 2012)

▸▸ At the start of the 65th World Health Assembly, WHO Chief Dr Margaret Chan said that in 2011, "…after extensive technical collaboration, WHO prequalified China's State Food and Drug Administration". She highlighted China's potential for increased vaccine production at lower prices following WHO approval of national vaccine regulator. Effective regulatory oversight is essential since vaccines are used on a population wide basis and are usually given to healthy infants. (*AllAfrica*, 21 May 2012)

Europe

▸▸ Gordon Brown is making a call for the international community to make education a higher priority and to develop a plan to achieve universal primary education by 2015. The former UK prime minister wants to create a "global fund for education", which would raise the GBP 13 billion per year needed to bring lessons to the poorest children. (*BBC News*, 25 Jan 2012)

▸▸ The French cabinet agreed to pursue a tax on financial transactions that they hope will eventually be adopted by other European countries. The project will see a 0.1% tax on buying shares belonging to firms with a French headquarters and more than one billion euros in capital. The French finance ministry estimates the tax, which if passed by parliament would take effect on August 1, will bring in € 1.1 billion (US$ 1.45 billion) annually. (*AFP*, 08 Feb 2012)

▸▸ In February, Norway announced a new initiative aimed at addressing gaps in the research on the importance of investment in female health as a particularly strong driver of sustainable economic development. This work will be undertaken under the auspices of a network of global leaders chaired by the Norwegian Foreign Minister Jonas Gahr Store and include representatives from key agencies, Bill and Melinda Gates Foundation, The Lancet, WHO and World Bank. (*NORAD*, 14 Feb 2012)

▸▸ Brian Greenwood has been named the winner of the Canadian Gairdner Foundation's 2012 Global Health Award for his "contributions to significantly reducing mortality in children due to meningitis and acute respiratory infection and for contributions to malaria prevention". His laboratory did the pivotal epidemiological studies that showed the importance of pneumonia and meningitis as major causes of death in young African children, a fact not widely appreciated at that time. His team consequently set up a series of trials of vaccines against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumonia* – the most frequent bacterial causes of pneumonia and meningitis in young African children. The success of two of these trials contributed to the decision by WHO to recommend immunisation with Hib and pneumococcal conjugate vaccines in countries with high child mortality. (*The Lancet*, 26 Mar 2012)

▸▸ A global initiative, designed to strengthen research into non-communicable diseases and improve collaboration between rich and poorer countries, has been launched in London. The Centre for Global Non-Communicable Diseases at the London School of Hygiene and Tropical Medicine aims to foster new studies and ensure research evidence is acted upon by policymakers. (*BMJ*, 25 Apr 2012).

India

▸▸ The Prime Minister Singh said that India will press science and technology into serving a national policy of more inclusive, sustainable and rapid growth for its people. Singh underscored the need to use innovations creatively for social benefit, and "give practical meaning to innovation". (*The Guardian*, 4 January 2012)

▸▸ India's pioneering "Home-based New Born Scheme" has shown the world a new way to cut down on neonatal mortality, which occurs within 28 days of birth. Almost 13 years after Dr Abhay Bang demonstrated a 62% reduction in neonatal mortality through multiple home visits in Maharashtra, the World Health Organization (WHO) has touted it as a global policy. (*Times of India*, 16 Feb 2012)

▸▸ More people in India own a mobile phone than a toilet at home, according to the latest census data. Nearly half of India's 1.2 billion people have no toilet at home; only

46.9% of the 246.6 million households have lavatories, while 49.8% defecate in the open and the remaining 3.2% use public toilets. (*BBC News*, 14 Mar 2012)

▸▸ Bill Gates and Uttar Pradesh's Chief Minister Akhilesh Yadav held a meeting in the state capital to define ways to improve the health and agriculture sector with the help of the Bill and Melinda Gates Foundation. It was decided that a memorandum would be signed between the state government and the Foundation, under which the Foundation would provide technical, management and program design support in the fields of maternal, neonatal, child health, vaccination and various other health and agriculture related areas. (*Economic Times*, 30 May 2012)

▸▸ The number of people with cancer is set to surge by more than 75% across the world by 2030, with particularly sharp rises in countries such as India, as they adopt unhealthy 'Westernised' lifestyles. A study published in *Lancet Oncology* predicted that middle-income countries could see an increase of 78% in the number of cancer cases by 2030. Cases in less developed regions were expected to see a 93% rise over the same period. Those rises would more than offset signs of a decline in cervical, stomach and other kinds of cancer in wealthier nations. (*Reuters*, 31 May 2012).

The Americas

▸▸ The definition of autism is being reassessed by an expert panel appointed by the American Psychiatric Association. Proposed changes in the definition of autism would sharply reduce the surging rate at which the disorder is diagnosed now. However, it may make it harder for many people who would no longer meet the criteria to get health, educational and social services. For years, many experts have been suggesting that the vagueness of the current criteria for autism and related disorders was contributing to the ballooning rate of 1% children being affected, according to some estimates. (*New York Times*, 19 Jan 2012)

▸▸ Gilead wants to be able to market Truvada, which is currently used as a HIV treatment, as a preventative pill to uninfected individuals. If approved, it would be the first of its kind. But the move has sparked debate among public health advocates who argue that the wide availability of the drug would discourage safe sex and would, in fact, increase the incidence of HIV. (*The Daily Mail*, 31 Jan 2012)

▸▸ The US President's budget request for 2013 proposed to cut the total money spent on global health initiatives by 3.5%, while PEPFAR's budget shrinks by 10.8%. However, contributions to the struggling Global Fund for AIDS, TB and Malaria should go up by 27%, to US$ 1.65 billion. In addition to the Global Fund, GAVI, IDA, Asian Development Fund and the African Development Fund are all among agencies that are getting increases on their funding; notably, GAVI by 11.5%. (*Center for Global Development,* 15 February 2012)

▸▸ Chagas disease, caused by parasites transmitted to humans by blood-sucking insects, has been named "the new AIDS of the Americas" in an editorial published in *PLoS Neglected Tropical Diseases*. The authors argue that the dangerous spread of Chagas through this hemisphere somewhat resembles the early spread of HIV. Chagas is also known as American trypanosomiasis, because the bugs carry single-celled parasites called trypanosomes. Like AIDS, Chagas disease has a long incubation time and is hard or impossible to cure. Chagas infects up to eight million people in the hemisphere, mostly in Bolivia, Mexico, Colombia and Central America; however, more than 300 000 of the infected live in the United States, many of them immigrants. (*New York Times*, 28 May 2012)

▸▸ Dr William Foege, who has been widely regarded as the health innovator behind the eradication of smallpox, has left an indelible mark in the field of global health. Because of his dedication and service to the public's health, President Barack Obama today presented him with the Presidential Medal of Freedom, the nation's highest civilian honour. (*Public Health Newswire*, 29 May 2012)

The Bill and Melinda Gates Foundation

Bihar Chief Minister Nitish Kumar was chosen by the Bill and Melinda Gates Foundation for its first Gates Vaccine Innovation Award for improving routine immunisation from 18.6% in 2005 to 70% in 2011. (*India.com*, 03 Jan 2012)

Bill Gates donated US$ 750 million to the struggling Global Fund to Fight AIDS, Tuberculosis and Malaria in January 2012. The donation was made as a promissory note intended to tide the fund over. Saudi Arabia recently made a contribution to the fund, and Brazil has followed Russia's lead among emerging nations in saying that it needed no further support for some health programmes. (*New York Times*, 26 Jan 2011)

The BMGF, government aid agencies, WHO, and 13 drug companies pledged nearly US$ 800 million and an increased drug supply toward a new push to wipe out 10 tropical diseases by 2020. The diseases, from leprosy to river blindness, affect 1.4 billion people worldwide. The companies have agreed even to open up their compound libraries – potential drug treatments that have gone through some tests – to the public-private partnership Drugs for Neglected Diseases Initiative (DNDi). (*Wall Street Journal*, 30 Jan 2012)

The Bill & Melinda Gates Foundation announced US$ 7.7 million in funding for 10 new grants to identify biomarkers for diagnosing tuberculosis (TB) in low-resource settings. This new grant program, Biomarkers for the Diagnosis of Tuberculosis, supports innovative research into TB biomarkers to facilitate the development of a simple low-cost tool that can quickly and accurately diagnose TB in low-resource settings. (*BMGF*, 09 Feb 2012)

Dr Cyrus Poonawalla of the Serum Institute in Hadapsar, India, revealed that the Bill & Melinda Gates Foundation may tie up with the Serum Institute to develop injectable polio vaccines. At present, The Global Alliance for Vaccine and Immunisation, Gates foundation and the Serum Institute are partners in several immunisation programmes around the world. The institute exports vaccines for GAVI projects, while the Gates Foundation funds clinical trials, Poonawalla said. (*Times of India*, 02 June 2012)

The GAVI Alliance

The GAVI Alliance recently decided to add HPV vaccines to its list of vaccines subsidized in the poorest countries, thanks in part to tiered pricing by the manufacturers; now it is feasible to seriously consider widespread sustained vaccination of populations in low-resource settings who do not have access to care (*Cancer Prevention Research*, 05 Jan 2012)

The GAVI Alliance said that as much as US$ 6.7 million intended for buying vaccines for children in poor countries was either stolen or misused. In Cameroon, as much as US$ 4.2 million was misused between 2007 and 2010, including US$ 1.8 million that is being investigated for theft, the GAVI Alliance announced in January 2012. As much as US$ 2.5 million was misused in Niger, of which US$ 1.5 million may have been stolen, the Geneva-based organization said. (*Bloomberg*, 19 Jan 2012)

US President Barack Obama and UK Prime Minister David Cameron have cited GAVI as a highly cost-effective, life-saving investment. At a joint press conference at the White House, the two leaders referred to last year's landmark pledging conference in London, where donors committed U$S 4.3 billion to help GAVI and its partners immunise an additional 250 million children and avert an estimated four million future deaths by 2015. (*GAVI Alliance*, 20 March 2012)

The GAVI Alliance has secured new prices with manufacturers for vaccines against rotavirus that are 67% lower than before. The bulk (95%) of the vaccines contracted – 132 million doses – will be procured at a cost of US$ 5 per (two dose) course instead of US$ 15, while the same course costs US$ 177 in the US. The deal will enable the Alliance to provide the vaccines to eight developing countries this year for some three million children. (*BMJ*, 11 Apr 2012)

GAVI Board Chair Dagfinn Høybråten said the appointment of three women to the GAVI Alliance Board "achieves a key target on gender". Her Royal Highness the Infanta Cristina of Spain, Dr Maria C. Freire, and Yifei Li took up their positions with immediate effect, resulting in 11 out of 26 Board members being women. In addition, Suraya Dalil, who has been approved by the Afghan Parliament as the new Minister of Public Health, is also a GAVI board member as of January 2012. GAVI's Board achieved its target of at least 40% representation for both genders within two years of approving guidelines at its meeting in July 2010. (*Center for Vaccine Ethics Policy*, 14 Apr 2012)

The World Bank

A free software program created by the World Bank researchers should assist staff and policy-makers in evidence-based decision making. The free software is especially valuable for analysts in developing countries. With built-in modern statistical technology and a user-friendly interface, ADePT empowers policy practitioners to conduct sophisticated economic analysis. It also serves as a platform for researchers to share findings. (*The World Bank*, 05 Jan 2012)

The World Bank has warned developing countries they need to be prepared for shocks as global economic growth slows. The organisation is now predicting a 0.3% contraction for the eurozone in 2012. The World Bank chief economist, Justin Yifu Lin, said that "...developing countries need to evaluate their vulnerabilities and prepare for further shocks, while there is still time". The World Bank is predicting growth of 5.4% for developing countries in 2012 and 1.4% for high-income countries, down from its forecasts of 6.2% and 2.7% respectively in June 2011. (*BBC*, 18 Jan 2012)

The World Bank is launching an innovative lending instrument that ties funding directly to the delivery of results. "Program-for-Results" will not provide financing to cover a program's expense. Instead, it will disburse money upon the delivery of predefined results. The World Bank is expected to channel 5% of its total portfolio through PforR. The CGD said this equates to some US$ 1 billion, or 20 projects per year, and the instrument will be assessed after the first two years. (*Devex*, 24 Jan 2012)

Ministers of Finance from the BRICS group of emerging market powerhouses – Brazil, Russia, India, China and South Africa – met on the sidelines of a G20 meeting in Mexico City and agreed the top World Bank job should be open to all countries. They agreed to reject the tradition that an American would automatically be selected to head the World Bank, and they will look at putting forward their own candidate for the open job. US President Barack Obama, however, nominated a Korean-American known for his work in fighting disease in impoverished countries. Jim Yong Kim, 52, is president of Dartmouth College, the former director of the Department of HIV/AIDS at the World Health Organization, and a founder of Partners in Health. He was appointed in mid-April. (*New York Times*, 16 Apr 2012)

Years after debt campaigners succeeded in persuading the International Monetary Fund (IMF), World Bank and G8 to abolish debts worth billions of dollars owed by developing countries, figures show total external debts are once again on the increase. Data in the World Bank's Global Development Finance 2012 report shows total external debt stocks owed by developing countries increased by US$ 437 billion over 12 months, to stand at US$ 4 trillion at the end of 2010, the latest period for which data are available. (*The Guardian*, 15 May 2012)

United Nations (UN)

In its annual report on global employment, the United Nations International Labour Organization (ILO) said that the world needs to create 600 million new jobs over the next decade to sustain economic growth and maintain social stability. The report, entitled 'Global Employment Trends 2012: Preventing a deeper jobs crisis', states that the world faces the additional challenge of creating decent jobs for the estimated 900 million workers who subsist on less than US$ 2 a day. (*UN News*, 23 Jan 2012)

Cases of dementia – and the heavy social and financial burdens associated with them – are set to soar in the coming decades as life expectancy and medical care improve in poorer countries, the UN's health agency (WHO) said in its World Dementia Report. Some 35.6 million people were living with dementia in 2010, but that figure is set to double to 65.7 million by 2030. "The numbers are already large and are increasing rather rapidly", said Dr Shekhar Saxena, the head of WHO's mental health division. (*Associated Press*, 11 Apr 2012)

The global campaign to fight malaria is appealing for US$ 3.2 billion to try to reach the UN goal of "near-zero" deaths from this mosquito-borne disease by the year 2015. There has been "great progress" in reducing malaria deaths using bed nets, insecticide spray and drugs, said Ray Chambers, the UN secretary-generals special envoy for malaria. (*Washington Post*, 24 Apr 2012)

A new United Nations initiative seeks to involve private businesses in helping developing countries tackle corrup-

tion and strengthen their ability to fight it. "Corruption has a disproportionate impact on poor communities and a corrosive effect on the fabric of societies across the globe", the Executive Director of the UN Office on Drugs and Crime, Yury Fedotov, said at the sidelines of the 21st Session of the Commission on Crime Prevention and Criminal Justice in Vienna, Austria. (*UN News*, 24 Apr 2012)

UN chief Ban Ki-moon declared in May 2012 that Britain's Prime Minister David Cameron, President Susilo Bambang Yudhoyono of Indonesia and Liberia's President Ellen Johnson-Sirleaf will lead a global panel to set international targets on sustainable development. The three leaders will represent the world's rich, middle- and low-income countries, and start their work after a major summit in Rio de Janeiro in June. (*AFP*, 09 May 2012)

UN-AIDS

South Africa is home to the highest number of HIV cases in the world. However, Sheila Tlou, UNAIDS regional director for East and Southern Africa, said that the country should see a massive reduction by the end of the decade after a sea-change in government policy. South Africa now has more people with HIV infections than any country in the world, with 5.6 million, because of a lack of political commitment in the past. However, Ms Tlou said that "... there is a turnaround in the new government under President Jacob Zuma, which is committed, and by 2020 there will be massive reductions in South Africa". (*AFP*, 19 Jan 2012)

The Russian State Research Center for Virology and Biotechnology, Vektor, has successfully completed the first stage of clinical trials of an HIV vaccine. The vaccine induces a strong antibody (antigen), as well as cellular response, said Vektor's director Alexander Sergeyev. The vaccine is now to be approved for the second stage of tests. (*RIA Novosti*, 06 Feb 2012)

Cuba's top biotech teams have successfully tested a new AIDS vaccine on mice, and are ready to soon begin human testing. At the bioconference in Havana, it has been announced that the vaccine TERAVAC-HIV-1 was made from recombinant proteins aiming "to cause a cellular response against the (HIV) virus". (*AFP*, 06 Mar 2012)

The United Nations Secretary-General Ban Ki-moon has issued his first report on HIV to the UN General Assembly since the 2011 High Level Meeting on AIDS. In the report, he highlighted "…the urgent need to achieve immediate, tangible results and for the AIDS response to be smarter, more strategic, more efficient, and grounded in human rights". (*UNAIDS*, 30 Apr 2012)

A recent study that evaluated US aid program aimed at helping foreign countries battle the AIDS epidemic showed that about 740 000 lives were saved from 2004–2008. The US President's Emergency Plan for AIDS Relief, or PEPFAR, was started by former president George W. Bush in 2003 with a five-year, US$ 15 billion investment in global AIDS in 15 countries. (*AFP*, 15 May 2012)

UNICEF

UNICEF is preparing ambitious plans to update, strengthen and vastly expand its global vaccination programme. (*UNICEF*, 03 Jan 2012)

According to the Humanitarian Action for Children 2012 report, launched at the end of January 2012, the ongoing crisis in the Horn of Africa will remain a significant part of UNICEF's global humanitarian response in the coming year. UNICEF asked for US$ 1.28 billion to meet the needs of the most vulnerable children and their families in 25 countries and territories – a 9% decrease from last year's appeal. (*UNICEF*, 26 Jan 2012)

UNICEF announced that it had joined the International Aid Transparency Initiative (IATI) to improve public accessibility to information on how aid is spent. UNICEF joints the World Bank, Britain's Department for International Development, the African Development Bank, the European Commission and others in the initiative. By creating common standards for sharing information about aid, IATI will make that information much more accessible to all. As part of its commitment to greater transparency and accountability, UNICEF will make public online the volume, allocation and results of development expenditure. (*UNICEF*, 13 Apr 2012)

The first-ever World Immunization Week took place from 21–28 April 2012. UNICEF offices around the world are engaging in immunization campaigns and raising

awareness about the importance of vaccines to child survival; UNICEF is the world's largest buyer of vaccines for the world's poorest countries, and has been supplying vaccines to children for over 50 years. (*UNICEF*, 24 Apr 2012)

A study commissioned by UNICEF in January 2012 showed that 46% of the 600 respondents participating in a baseline Knowledge, Attitude and Practices (KAP) study are ignorant about vaccination being a way to prevent polio, while only one in three parents is concerned that their child is at risk of contracting polio this year. (*The News/Pakistan*, 05 June 2012)

World Health Organization (WHO)

The World Health Organization Executive Board agreed to propose to the World Health Assembly the establishment of a mechanism for international collaboration on counterfeit and substandard medical products, but with the exclusion of trade and intellectual property issues. One of the contentious issues around counterfeit drugs has been the suspicion on the part of some developing countries that concerns about counterfeit and substandard medicines are being purposely confused with trade in legitimate generic medicines from those countries. Removing intellectual property and trade from WHO discussions likely minimises the possibility of confusion. (*IP–Watch*, 28 Jan 2012)

Organisations working to combat non-communicable diseases worldwide say that the timetable for developing crucial targets "cannot afford to slip". Ms Judith Watt, interim director of the Non-Communicable Disease Alliance, which represents non-governmental organisations and other civil groups, said it was vital that the World Health Organization fulfil its commitments this year to recommending voluntary global targets for the prevention and control of non-communicable diseases. (*BMJ*, 30 Jan 2012)

On World Health Day (7 April), WHO is calling for urgent action to ensure that people reach old age in the best possible health. In the next few years there will be more people in the world aged over 60 than children aged less than five, for the first time in human history. By 2050, 80% of the world's older people will be living in low- and middle-income countries. (*WHO*, 03 Apr 2012)

The World Health Organisation (WHO) has warned that a third of the world's population is carrying tuberculosis, and the disease could become incurable if governments fail to act. Lack of funding for public health programmes, the sale of inaccurate blood tests, and the misuse of drugs, particularly in the private health sector, are hampering the fight against the disease and leading to drug resistance. (*The Independent*, 13 May 2012)

The World Health Organization nominated its current chief Margaret Chan for a second term at the Director General of the WHO. Ms Chan was the only candidate put forward to the WHO's executive board, who made the official nomination at a meeting in Geneva. She was re-elected in May 2012, at the World Health Assembly. (*Associated Press*, 25 May 2012)

Environment

The 18 past winners of the Blue Planet prize – which is the unofficial Nobel prize for the environment – warned in February that civilization is faced with a "perfect storm" of ecological and social problems, driven by overpopulation, overconsumption and environmentally malign technologies. In the face of an "absolutely unprecedented emergency", they said that society had "no choice but to take dramatic action to avert a collapse of civilization". (*The Guardian*, 20 Feb 2012)

A traditional root crop long neglected by modern science could be the best bet for farmers in Sub-Saharan Africa to beat climate change, according to a new study published in a special edition of Tropical Plant Biology. This study found that the rugged root crop cassava could brush off expected temperature rises of up to 2°C in the region by 2030 – and could be even more productive thanks to climate change. (*AllAfrica*, 28 Feb 2012)

Speaking in Bangkok at the Southeast Asia launch of the IPCC special report on managing the risks of extreme events and disasters, Rajendra K. Pachauri, chief of the Intergovernmental Panel on Climate Change (IPCC), said that "…The world can no longer ignore the facts about climate change and its link to human society". He added that "…some facts which are incontrovertible need to be accepted by the public". Pachauri said he believed the upcoming Rio +20 sustainability conference in June 2012 would lead to new agreements that could help shift the world onto a path of more sustainable development. (*AlertNet*, 04 May 2012)

According to a new report from the United Nations Environment Programme, tens of millions of new jobs could be created around the world in the next two decades if green policies are put in place to switch the high-carbon economy to low-carbon. The report estimated that between 15 and 60 million additional jobs would likely be created as net gains in employment for the world economy, taking into account any job losses in high-carbon industries. As well as generating net new gains in the number of jobs, the switch to a green economy could help to lift millions of people out of poverty. (*The Guardian*, 31 May 2012)

The UN's Environment Programme sounded the alarm in its fifth Global Environment Outlook (GEO-5) report, published two weeks before the Rio +20 summit in Brazil, one of the biggest environmental meetings in years. Population growth, urbanization and consumption are set to inflict irreversible damage on the planet, and the UN called for urgent agreement on new environmental targets at an Earth summit in June 2012. Only a few hours after GEO-5's release, the journal *Nature* published a review of scientific evidence on environmental change concluding that the biosphere – the part of the planet that supports life – "… could be heading for rapid, possibly irreversible change". (*Reuters*, 06 Jun 2012)

Demography

India is the most dangerous place in the world to be a baby girl. Newly released data shows that an Indian girl child aged 1-5 years is 75% more likely to die than an Indian boy, making this the worst gender differential in child mortality for any country in the world. (*Times of India*, 01 Feb 2012)

The call to invest in adolescent girls has been voiced within the development field in recent years, supported by the UK Department for International Development (DfID), the World Bank and several UN agencies. "Girl effect" proponents argue that if girls in developing countries delay childbearing they will be significantly better off. However, this argument is based on questionable evidence, because the causal role of early childbearing in poverty has not been convincingly demonstrated. (*The Guardian*, 10 Feb 2012)

A major report from the UK Royal Society suggested that the World population needs to be stabilised quickly, and high consumption in rich countries rapidly reduced, to avoid "…a downward spiral of economic and environmental ills". Their assessment of humanity's prospects in the next 100 years, which has taken nearly 2 years to complete, argued strongly that to achieve long and healthy lives for all 9 billion people expected to be living in 2050, the entangled issues of population and consumption must be pushed to the top of political and economic agendas. (*The Guardian*, 26 Apr 2012)

Last year, the world population reached 7 billion, adding the last billion in merely 12 years. Despite this rapid growth, the predictions about the potentially disastrous consequences of rapid population growth have not materialized; in fact, various summary measures of individual well-being have in fact increased. From 1960 to 2010, global life expectancy increased from 51.2 to 67.9 years, infant and maternal death rates declined substantially, education and levels of female schooling increased, global per

capita food production and consumption rose, and the proportion of the global population living in poverty declined significantly. (*Slate*, 03 May 2012)

▸▸ According to the United Nations, about 3.4 billion people live in urban areas – about half of the world's population – but nearly a third of them, or about one billion, live in slum conditions. By 2030 that number is likely to double, unless living conditions improve. Concern has been mounting so much about the situation that the *Lancet* has set up a Commission on Healthy Cities to look at what should be done. (*BBC News*, 30 May 2012)

Economy

▸▸ After a decade of rapid economic growth, many developing countries have attained middle-income status based on increase in their overall GDP, but poverty reduction has not kept pace with their GDP growth. As a result, most of the world's poor – up to a billion people – now live in these new middle-income countries (MICs), making up a "new bottom billion", shifting the majority of the global disease burden into MICs. This poses a challenge to global health agencies, which are accustomed to disbursing funds on the assumption that the majority of poor people live in poor countries. (*Center for Global Development*, 10 Jan 2012)

▸▸ Ratings agency Moody's maintained France's top AAA credit rating for now, but the country was downgraded by another agency, Standard & Poor's (S&P). Moody's said it would update its position on France later this quarter. It is feared that downgrading of France's credit rating would further increase debt worries across Europe. (*BBC*, 16 Jan 2012)

▸▸ The World Bank (WB) at the end of February 2012 that the share of people living in extreme poverty around the world continued to decline in recent years, despite financial crises and surging food prices. The WB's preliminary estimates for 2010 showed that the world's extreme poverty rate – people living below US$ 1.25 a day – had fallen to less than half of its 1990 value, meeting the first UN's Millennium Development Goal of halving extreme poverty from its 1990 level before its 2015 deadline. In 2008, about 1.29 billion people – roughly 22% of the developing world's population – had less than US$ 1.25 a day to make their living, whereas 17 years earlier 1.94 billion people lived in extreme poverty. These estimates are based on more than 850 household surveys in about 130 countries. The region with the highest extreme poverty rate was Sub-Saharan Africa, where about 47% of the population had below US$ 1.25 a day to live. (*Wall Street Journal*, 29 Feb 2012)

▸▸ Recently, 65 world-renowned researchers, economists and Nobel laureates got together to answer what would they do if they had US$ 75 billion and four years to improve the world's well-being. They released their findings in April this year, after more than a year of reviewing proposals and evidence, thanks to the Copenhagen Consensus Center. Being economists, they weighed their choices carefully using cost-benefit analyses. Seventy-five billion dollars represents a 15% annual increase on top of the current investments of developed nations in foreign aid. They agreed that child nutrition is the "best buy" in development today. (*Copenhagen Consensus Center*, Apr 2012)

▸▸ The idea that an infusion of hope can make a big difference to the lives of poor people was the central idea of a lecture at Harvard University by Esther Duflo, an economist at the Massachusetts Institute of Technology known for her data-driven analysis of poverty. Ms Duflo argued that the effects of some anti-poverty programmes go beyond the direct impact of the resources they provide. They make it possible for the very poor to hope for more than mere survival. (*The Economist*, 12 May 2012)

Energy

▸▸ The International Year of Sustainable Energy for All kicked off in January 2012. United Nations officials called on governments, the private sector and civil society to help expand access to energy, improve efficiency and increase the use of renewables. Globally, one person in five still lacks access to modern electricity, while three billion people still use wood, coal, charcoal, or animal waste for cooking and heating. UN Chief Mr. Ban attended the opening of the World Future Energy Summit, which is taking place in Abu Dhabi, United Arab Emirates. (*UN News*, 16 Jan 2012)

▸▸ A new UN report suggests that women should be the focus of efforts to bring access to modern energy to those who lack it, as "...bringing energy to women and girls helps lift communities out of poverty and improves health". But the report also warned that providing energy alone was not enough to combat poverty. Programmes to provide energy access work best when they are paired with access to other key services, such as education and microfinancing. (*The Guardian*, 19 Jan 2012)

Royal Dutch Shell and other natural resources companies have stepped up efforts to counteract planned anti-corruption rules that would force them to disclose payments to governments in countries where they operate. Bill Gates recently threw his weight behind a proposed rule included in the Dodd-Frank act, which would require US extractive companies to disclose similar payments. (*Financial Times*, 19 Feb 2012)

US-based *d.light* design company was one of the pioneers in distributing rugged solar lamps and lanterns, and now distributes its products in 40 countries, focusing particularly on Sub-Saharan Africa and India. In just five years, the company has distributed more than 1.4 million lanterns, ranging in price from about US$ 10 for a student lamp to about US$ 45 for a rugged, handheld lantern with four light settings and cell-phone charger. A partnership with the Shell Foundation is aimed at implementing market awareness programs and supporting local entrepreneurship. Donn Tice, chief executive officer, said that "… while *d.light* is a for-profit company, it has a social mission to help people replace kerosene lanterns, cheap flashlights and other throwaway items with safer, cleaner, more permanent lanterns." (*National Geographic News*, 06 Jun 2012)

The poll by the AP-NORC Center for Public Affairs Research showed that, when it comes to saving energy, people in the United States know that driving a fuel-efficient car accomplishes more than turning off the lights at home, but that doesn't mean they'll do it. A new poll shows that while most of those questioned understand effective ways to save energy, they have a hard time adopting them. Six in 10 surveyed say driving a more fuel-efficient car would save a large amount of energy, but only 1 in 4 says that's easy to do. People also are sceptical of carpooling or installing better home insulation, rating them as effective but impractical. On the other end of spectrum, 8 in 10 say they easily can turn off the lights when they leave a room, and 6 in 10 have no problem turning up the thermostat in summer or down in winter, although fewer than half think those easy steps save large amounts of energy. (*KnoxNews*, 09 Jun 2012)

Peace and Human Rights

About 200 million people around the world use illicit drugs. Cannabis users comprise between 125–203 million, users of opioids (heroin and morphine), amphetamines or cocaine total 15–39 million; and those who inject drugs numbered between 11–21 million. Ecstasy, LSD, non-medical use of prescription drugs and anabolic steroids are not included in this estimate. (*The Lancet*, 06 Jan 2012)

A rising proportion of abortions worldwide are putting women's health at risk. The World Health Organization study estimates that global abortion rates are steady, at 28 per 1000 women each year. *The Lancet*, which published the study, characterized the figures as "deeply disturbing". (*BBC News*, 19 Jan 2012)

UN human rights experts have expressed their dismay at what they see as the continuing abuse of anti-terrorism legislation to curb freedom of expression in Ethiopia. The blunt criticism from the UN comes after a Human Rights Watch also accused the government of forcibly relocating thousands of people in the Gambella region. (*The Guardian*, 03 Feb 2012)

The global arms trade has grown by nearly a quarter over the last four years, with new growth mainly in poorer countries. India is now officially the world's biggest importer of arms. (*The Guardian*, 19 Mar 2012).

The UN refugee agency predicted that the number of people fleeing their homes and becoming refugees or displaced in their own countries will increase in the next 10 years. This will come as a result of a multitude of complex causes, ranging from conflict and climate change to population growth and food shortages, according to their report. (*Associated Press*, 01 Jun 2012)

Food, Water and Sanitation

Jose Graziano da Silva of Brazil, the new FAO Chief from the start of 2012, said that volatility in food markets was likely to continue and that prices "will not be going up as in the last two to three years but will also not drop down". (*Reuters*, 03 Jan 2012)

The United Nations World Food Programme (WFP) is launching a week-long campaign in early February, during which users of the popular online trivia game 'Freerice' can recruit their friends to help bring food to the world's most vulnerable populations. Under its theme '6 Degrees of Fre-

erice', fans of the game are being asked to recruit six friends to join in the online fight against hunger. (*UN News*, 01 Feb 2012)

Better access to water and sanitation is crucial to reducing maternal mortality and achieving Millennium Development Goal 5, according to a group of scientists from McMaster University in Canada. The impact of unsafe water and sanitation on the death rates of children under the age of five and mothers in the year after childbirth have been quantified for the first time. (*Environmental Health*, 17 Feb 2012).

It has been estimated that alcohol kills more than 2.5 million people annually, more than AIDS, malaria or tuberculosis – making it one of the world's leading killers. For middle-income people, who constitute half the world's population, alcohol is the top health risk factor, greater than obesity, inactivity and even tobacco. (*Scientific American*, 15 Feb 2012)

The UN announced that international target to halve the number of people who do not have access to safe drinking water has been met five years before the 2015 deadline. According to the WHO and UNICEF's joint monitoring programme for water supply and sanitation (JMP), between 1990 and 2010 more than 2 billion people gained access to improved drinking water sources, such as piped supplies and protected wells. Using data from household surveys and censuses, 89% of the population – 6.1 billion people – now used improved drinking water sources at the end of 2010, 1% more than the 88% target contained in Millennium Development Goal 7 (MDG7), set in 2000. (*The Guardian*, 06 Mar 2012)

Science and Technology

Tiny capsules engineered to mimic part of the body's immune system could strengthen its response to vaccines. The nanoparticles, described in the journal Nature Materials, are a message sent from cells in the skin to warn of a threat. Scientists from Duke University in the USA said mice given them as part of a vaccine coped with otherwise lethal infections. They could soon be suitable for humans, too. Vaccination involves priming the immune system to recognise particular bacteria or viruses, so that it is ready to counter-attack quickly in the event of a genuine infection. (*BBC News*, 22 Jan 2012)

A two-year study of nearly 200 000 American girls and women aged 9 to 26 showed that those who received the HPV vaccine Gardasil were not at a greater risk for 16 different autoimmune disorders. (*PressTV*, 29 Jan 2012)

The full details of recent experiments that made a deadly flu virus more contagious will be published, despite recommendations by the United States that some information be kept secret for fear that terrorists could use it. The WHO announcement made in February followed two months of heated debate about whether the results of the research should be published. Anthony S. Fauci, director of the US National Institute of Allergy and Infectious Diseases, said that "…the group consensus was that it was much more important to get this information to scientists in an easy way to allow them to work on the problem for the good of public health". WHO spokesman Gregory Hartl told Reuters that "…there must be a much fuller discussion of risk and benefits of research in this area and risks of virus itself". Critics said this was a closed meeting, dominated by flu people who have a vested interest in continuing this kind of work. (*New York Times*, 18 Feb 2012)

The number of patents filed by large pharmaceutical companies has dropped significantly in recent years. This suggests intensifying problems for the industry to maintain the pipeline of new products over the coming decade. There is also a shift from 'small molecules', or chemical-based medicines, to those that are biological and which comprised 60% of the total by 2009. (*Financial Times*, 18 Mar 2012)

Researchers at Texas A & M University have genetically engineered a goat so it creates malaria vaccine in its milk. Their research is still in a preliminary stage and requires the analyses of safety and effectiveness. Their idea would be to place vaccine producing goats in villages around Africa, so that people could simply drink goats' milk and get immunized. (*Care2*, 16 Mar 2012)

The importance of a common global health definition: How Canada's definition influences its strategic direction in global health

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In late 2011, the Expert Panel on Canada's Strategic Role in Global Health (herein: the panel) selected a global health definition for Canada. This decision is significant as the chosen definition forms the foundation of the panels forthcoming recomended role for Canada in global health. In turn, the global health community can draw lessons from Canada's decision to inform their own understanding of the term and demystify priority setting. In this paper we examine the five definitions considered by the panel and analyze the core characteristics of each in order to understand the rationale for the final choice as well as the implications of the chosen definition. To understand the basis upon which Canada will build its strategic direction for global health it is useful to frame this analysis in light of the other short-listed definitions.

WHY IS THE DEFINITION OF GLOBAL HEALTH IMPORTANT?

There has been a tremendous amount of discussion about global health without rooting the term itself to a common definition. Countless books and journal articles have been written and university programs have been designed around global health without a definition of the term. There are numerous examples of work being done in this field without a clear definition in place [29,30]. Indeed, it is often not clear how people and organizations engaged in global health are using the term. An analogy would be for a medical team to discuss an intervention for a patient with condition 'x', without an agreed-upon definition of the condition itself. Because global health is composed of, and relies on, multiple disciplines and sectors of society – which work from different languages, values, motivations and perspectives – it is important that at the very least there be a clear communication of what each actor is referring to when they use the term global health. For actors to write, instruct or develop meaningful strategies for global health, they require a definition of global health. This definition can be used as a frame from which to work and can be communicated to others.

BACKGROUND

Current global health trends, including epidemiological and demographic transitions, the rising burden of disease, climate change and the increasing awareness of global disparities in health, have heightened interest in the field of global health among the international medical and public health communities [1-4]. Yet, there is a considerable amount of ambiguity and controversy about what 'global health' means [5,6].

In September 2010, the Canadian Academy of Health Sciences, with the assistance of the Council of Canadian Academies, brought together 15 Canadian global health experts to form the Expert Panel on Canada's Strategic Role in Global Health [7,8]. The panel was tasked with assessing whether Canada ought to play a more strategic role in global health and, if so, to identify potential roles [7]. According to the Canadian Academy of Health Sciences, "Canada does not have a national multi-sectoral strategy to address the increasingly complex issue of global health" [7]. In order to frame deliberations about potential strategic roles for

In a report published by the Expert Panel on Canada's Strategic Role in Global Health, the panel selected a global health definition for Canada. As the definition chosen by the expert panel provides the foundation from which Canada identifies its strategic roles in global health, understanding the definition sheds light on the trajectory and future role of Canada in the global health field. The decision also signals to the international global health community the likely future direction for Canada's global health initiatives.

Canada in global health, the expert panel felt a common definition of global health was necessary [7,9]. Each of the five definitions had been widely disseminated in leading peer-reviewed health journals or had been developed by key actors in the research and practice of global health [9].

In the November 2011 report, *Canadians Making a Difference*, the panel indicated the Koplan et al. (2009) definition was agreed upon as the common definition for global health (**Table 1**) [7,12]. The purpose of this essay is to outline an approach for evaluating global health definitions in order to ultimately select the most appropriate definition. In this paper we analyze the five definitions short-listed by the panel of Canadian global health experts [8], we deconstruct the characteristics of each and consider the implications on strategic priorities and initiatives of including or excluding these characteristics in a definition of global health.

The characteristics of each definition were identified by inductive analysis, which allows characteristics to emerge from patterns found in the definitions being examined without presupposing what these characteristics will be [15]. We read and analyzed the definitions independently in order to identify distinct characteristics and to consider their role in a definition of global health (**Figure 1**). Consensus on the characteristics was reached through group discussion of both the definitions and potential examples of the different characteristics. The definitions were then coded for the occurrence or non-occurrence of each characteristic [9].

We determined whether a characteristic is primary or secondary by examining how it is portrayed in the literature. Primary characteristics are those that the global health grey and peer-reviewed literature portray as essential to a con-

Table 1 Inductive analysis of global health definitions

	Primary characteristics				Secondary characteristics			
Equity	Global conceptualization	Causes	Means	Solutions	Source of obligation	Multi-disciplinary	Actors	Reactive (R) Proactive (P)
Brown: "Global health" in general, implies consideration of the health needs of the people of the whole planet above the concerns of particular nations. The term "global" is also associated with the growing importance of actors beyond governmental or intergovernmental organizations and agencies.[10]								
No	**Yes**	**No**	**No**	**No**	**No**	**No**	**Yes**	**No**
European Commission: Global health… is about worldwide improvement of health, reduction of disparities, and protection against health threats. [11]								
Yes	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**P**
Koplan: Global health is an area of study, research, and practice that places a priority on improving health and achieving equity in health for all people worldwide. Global health emphasizes transnational health issues, determinants, and solutions; involves many disciplines within and beyond the health sciences and promotes interdisciplinary collaboration; and is a synthesis of population-based prevention with individual-level clinical care. [12]								
Yes	Yes	Yes	Yes	Yes	No	Yes	No	R+P
United Kingdom: Global health refers to health issues where the determinants circumvent, undermine or are oblivious to the territorial boundaries of states, and are thus beyond the capacity of individual countries to address through domestic institutions. Global health is focused on people across the whole planet rather than the concerns of particular nations. Global health recognizes that health is determined by problems, issues and concerns that transcend national boundaries.[13]								
No	Yes	Yes	No	No	Yes	No	No	No
U.S. Institute of Medicine: Global health is the goal of improving health for all people in all nations by promoting wellness and eliminating avoidable disease, disability, and death. It can be attained by combining population-based health promotion and disease prevention measures with individual-level clinical care.[14]								
Yes	Yes	No	Yes	Yes	No	No	No	R + P

cept of health that is differentiated as global. Without these characteristics, the term global health would cease to be distinct from other areas of health or it would be too vague to be actionable. Secondary characteristics are those mentioned in the literature that add detail or fine-tune the concept but are not regarded as crucial to the distinctiveness of global health or necessary for clarity.

PRIMARY AND SECONDARY CHARACTERISTICS OF GLOBAL HEALTH DEFINITIONS

Through the initial inductive analysis of the definitions, we identified five primary characteristics and four secondary characteristics overall (**Table 1**).

PRIMARY CHARACTERISTICS

The five characteristics considered *primary* are noted in the left side of **Table 1**.

1. Equity

The book, *Global Health and Global Health Ethics,* states that "the most striking feature about the state of global health is that it is characterized by such radical inequities" [5]. Indeed, basic statistics on inequities in health status and access....." provide the background of global health work. The lifetime risk for a Canadian woman dying from pregnancy complications or childbirth is 1 in 11 000 [5]; the lifetime risk for a woman in Niger is 1 in 7 [5]. Similarly, life expectancy at birth varies by over 50% depending on the country of birth. For those born in Canada or Japan, the average life expectancy is 80 years or more, whereas in Afghanistan and Sierra Leone life expectancy is approximately 40 years [5]. While a Canadian child diagnosed with acute lymphoblastic leukemia has a 90% chance of being cured; in the poorest countries of the world more than 90% of children diagnosed with this disease will die [16]. This is the context in which global health is practiced today.

Faced with such appalling disparities, much of global health research and practice is based on the underlying notion of equity [17,18]. In the past, international health focused on understanding "the other" or "the tropical" and was largely shaped in the context of colonialism. Today, the forces of globalization and the information and communication revolution have brought glaring global health disparities into full view and are the lens through which much of global health work is done. As a result, 'equity' was listed by the expert panel as the first of three core principles that will guide the global health strategic vision for Canada, along with effectiveness and engagement [7]. Thus, it is telling that the expert panel chose a definition that not only includes the principle of 'equity', but one that emphasizes it in the very first sentence.

2. Global conceptualization

A global conceptualization, differentiable from an international or supra-national perspective, is an integral component of a global health definition [19]. 'Global' health goes beyond the nation and focuses instead on vulnerable populations worldwide [6]. The difference between the terms international and global may appear small at first, however, the implications are profound and at the very heart of the practice of global health and therefore also its definition. While international refers to nations interacting with nations, and supranational suggests bodies above the national level, global implies ignoring borders altogether and bridging gaps between need and care wherever they may exist. This is not to say that borders are porous or nations unimportant. National governments continue to provide the bulk of funding for development assistance in health, although the channels through which they are funneled are increasingly becoming global actors – such as the Global Fund and the Bill and Melinda Gates Foundation [20]. What is truly 'global' is the conceptualization of health itself, represented by the goal of health for all people, irrespective of location or nationality. Not surprisingly, all five of the definitions considered by the expert panel embrace a global conceptualization and refer to the goal of "health of all people" or health for "people worldwide".

3. Causes

Causes are the contextual factors that determine a health issue. Causes can include the social, economic and physical environment, as well as individual characteristics and behaviors [21]. This characteristic highlights the fact that global health is not only a field of study or practice but also a response to a burgeoning set of upstream challenges. Understanding the causes of these challenges is crucial for addressing global health status, and also for distinguishing its practice from humanitarian aid. Many of the biggest global health challenges are intimately tied to socio-political and economic forces related to resources, eg, famines; health infrastructure and skilled worker shortages; and access barriers to essential medicines, vaccines and health services. Thus to ignore the causes of global health challenges – in the field and in the definition – is to miss the very reason for the existence of the field. The challenges and disparities in global health are the *raison d'être* for the research, study and practice of global health. Unlike a science or an art, the field of global health is very much about providing solutions to current problems. As such, it would be short-sighted not to consider the causes of global health problems in order to better formulate the solutions. Thus the causes ought to be included in a comprehensive and complete definition of the field. Specifying causes narrowly or broadly will either focus or widen the scope of factors to be addressed in global health activities.

Photo: Courtesy of Alasdair Campbell, personal collection

4. Means

Means are the methods and paths through which health activities take place. Depending on the conceptualization of global and the scope of causes, the means may range from providing individual-level clinical care or community education, through population-level disease prevention, to large scale national or international interventions [6]. Specifying the means pushes the concept from descriptive to prescriptive, or from 'what' to 'how' global health 'should' be carried out. Global health is not only a field of study but also a field of practice. Excluding *means* from the definition of global health would render it incomplete.

5. Solutions

Solutions are the activities undertaken to address health issues. The range of potential solutions varies with the extent of available resources, political will, time frame and scope of goals [22,23]. Solutions to global health challenges can, and often do, come from multiple sectors of society including the public system, academia, civil society and the private sector. Specifying global health solutions will guide priority setting for resource allocation under global health initiatives [24]. Decisions about solutions addressing imminent health problems will take precedence over investing in future health system capacity or tackling determinants of health [25,26]. Global health is about understanding the *causes* and finding the *means* to provide *solutions* to the challenges and disparities in health status of people worldwide. Thus solutions are a crucial component of a global health definition because they signal the fact that global health is not just a study or a practice, but a means to an end goal: the end of unnecessary, preventable and treatable inequities in global health status. Without including the solutions in the definition, the field and the definition lose the glue that holds it all together since there would be little use of studying or practicing global health, with its accompanying disparities and challenges, if global health practitioners were not interested in providing the solutions to said challenges. Thus we consider *solutions* an essential component of a global health definition.

SECONDARY CHARACTERISTICS

The four characteristics considered *secondary* are noted in the right side of Table 1.

1. Source of obligation

One of the examined definitions [13] refers to the source of obligation for global health activity. Specifically, resource-rich entities are obligated to help those with fewer resources tackle their health problems. This characteristic is part of the extensive ethical discussion on obligations [5], as the source and nature of obligations have implications for conceptualizations, means and solutions in global health. Nevertheless, for a working definition, obligation is adequately reflected in the primary characteristics. Specifically, the motive of global health is reflected in the shared desire to find solutions to challenges; while the feelings of or sources of obligation will undoubtedly vary across individuals and actors and cannot be summed up for the entire field and all those who practice or study it.

2. Multidisciplinary approach

The primary characteristics of a global health definition – that it crosses borders, has a multitude of causes and involves a range of means and solutions – implies the need for multiple professionals and disciplines in addition to medical professionals [27]. Although many global health issues require a multidisciplinary approach (for example, access to affordable antiretroviral treatments or implementing tobacco control strategies) it need not necessarily be so. Involving multiple disciplines all the time may not be necessary or efficient. A multidisciplinary approach is often, but not always, needed and beneficial and is therefore not an essential component of the field of the definition.

3. Actors

Typically, global health issues are large, complex, and dynamic. Just as multiple disciplines may be required, the nature of global health issues also often leads to multiple

actors using a variety of means to achieve different goals. Although the composition, funding mechanisms, values and goals of actors are important to the study and practice of global health [28], currently any individual or group can be an agent of global health. The all-inclusive nature of the work means that defining actors is not essential to the definition, though it is part of specifying means and solutions.

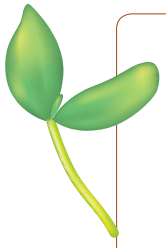
4. Reactive/proactive

Determining whether the provision of global health should be reactive, proactive or a combination of both depends on whether the focus is put upon current crises or future events that may result in crises. In a reactive approach, we respond to issues already at a crisis point when harm is likely already occurring and immediate solutions, such as famine relief, are required. A proactive response involves more foresight, for example, devising crop varieties adapted for climate change [2]. Determining a reactive, proactive or blended approach to action on a global health problem will direct resources to the most appropriate mix of solutions. These characteristics are descriptive of the means, the solutions, and the approach that is taken by global health actors; but are not descriptive of the field, and therefore not an essential part of the definition.

While it would be difficult to reach agreement upon a single, international definition of global health, nation-level common definitions could assist in anticipating and coordinating strategies and initiatives across regions and sectors. The European Union has identified and communicated their definition of global health [11] and the Expert Panel on Canada's Strategic Role in Global Health selected the Koplan et al. [12] definition as the base for decision making in Canada.

Now that this definition is in place, it can provide direction to academics and organizations working in the field. A different choice would have significantly altered the practice of global health in Canada from the path set by the chosen definition. For example, by picking a definition that includes equity, it indicates that under Canadian global health strategies equity is an essential component. Had the expert panel selected the Brown definition [10], which does not include equity, it would have indicated that equity was not a primary concern from the Canadian perspective on global health. This would have had enormous implications for the future practice and study of global health in Canada.

With the chosen Canadian definition for global health the expert panel has provided the international global health community, researchers and policy makers an indication of future directions for Canadian global health initiatives. It would benefit the international global health community to have all international actors working in the field clearly indicate their own understanding of the term global health and the definition that frames their work.



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Mental health spillovers and the Millennium Development Goals: The case of perinatal depression in Khayelitsha, South Africa

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Mental illness currently ranks among the top ten causes of burden of disease in low-income countries [1]. In the African region specifically, neuropsychiatric disorders account for approximately 5% of disability-adjusted life years lost, with nearly one-quarter of this burden attributable to unipolar depressive disorders [1].

Furthermore, this burden is projected to increase by 2030 [2]. There is accumulating evidence on the potential public health impact of scalable mental health treatments involving non-psychiatrists [3-5], with more studies under way [6-8], but overall the prevention and treatment of mental disorders have been relatively neglected in the global agenda [9,10].

> Based on our experience conducting research in a high-risk, peri-urban setting near Cape Town, South Africa, we estimate that perinatal depression is responsible for up to 14-32 percent of cases of child underweight in this community.

A substantive portion of the burden of mental disorders in low-income countries is thought to be attributable to many of the failures of human development as targeted through the Millennium Development Goals (MDGs), including poverty, HIV, and gender inequality. The evidence on depressive disorders and depressed mood is most well developed in this respect (see **Figure 1**). Depression has been associated with economic deprivation, especially in low-income countries and with regards to specific indicators of deprivation such as food insecurity [12,13]. Depression is also a known consequent of poor physical health [14]. And finally, gender inequality [15], often manifested starkly as violence against women in low-income countries [16], is commonly conceptualized as a risk factor for poor mental health among women [17].

If these relationships were causal and unidirectional, then interventions targeting MDG indicators related to poverty, HIV, and gender inequality would be expected to reduce the burden of disease from mental disorders. However, some of these relationships are bidirectional, suggesting that scaling up interventions to improve mental health may support efforts to achieve the MDGs. Emphasizing these spillover effects on other health outcomes of greater political interest may be one effective strategy to build support for mental health programming [18]. For example, depressive disorders and depressed mood are associated with significant psychosocial disability resulting in reduced economic productivity [19]. Depressed mood among women in the postnatal period has been associated with elevated risks for diarrhea and poorer growth among

their newborn infants [20-23]. And, among persons living with HIV/AIDS, psychological stress and poor mental health have been associated with reduced adherence to HIV antiretroviral therapy [24] and worsened HIV-related outcomes [25].

ADDRESSING PERINATAL DEPRESSION TO IMPROVE CHILD HEALTH

In order to concretely illustrate the potential contribution of mental health programming to achieving MDG targets, we sought to estimate the total burden of poor child health attributable to perinatal depression. To do this, we drew on our own experience conducting research on perinatal depression in Khayelitsha, a high-risk, peri-urban setting near Cape Town, South Africa (**Table 1**). In several studies we have conducted in this community, the prevalence of women meeting screening criteria for clinically significant depressive symptoms has ranged from 32–47% in the antenatal period [7,26-28] and 16–35% in the postnatal period [29-32]. Other researchers have employed similar methodologies and have obtained similar prevalence estimates [33,34]. The relevance of maternal mental health for child health has been demonstrated in a series of longitudinal studies showing that probable depression among mothers is associated with an approximately 2-fold increased risk of underweight status among their children [20-23].

Given the high prevalence of perinatal depression and the strong association between perinatal depression and child underweight, it is clear that perinatal depression constitutes a substantial contributor to the burden of child underweight in peri-urban Cape Town. If, borrowing from the previously cited studies, we assume that perinatal depression and child underweight are associated with a relative risk of 2 and that the prevalence of perinatal depression ranges from 16–47% (**Table 1**), then we can apply standard formulas to obtain a population attributable risk (PAR) estimate ranging from 14–32%. If perinatal depression is causally related to child underweight, these estimates suggest that it is responsible for up to 14–32% of cases of child underweight in this community.

> Estimating the extent to which prevention and treatment of mental disorders potentially increase the probability of achieving indicators of political importance can capitalize on greater support for these other health goals. Doing so, however, has the unattractive potential for instrumentalizing the alleviation of mental suffering and undermining concern for mental suffering for its own sake.

Further extrapolation to estimate the child mortality burden in South Africa that could be eliminated through successful scale-up of prevention or treatment of perinatal depression would require additional assumptions about the relationships between underweight and mortality, as well as about intervention efficacy in this context. However, given that approximately one-half of deaths of children under the age of five can be attributed to underweight [35-37] and that less than one-third of persons in South Africa with a severe mental disorder are estimated to be receiving needed care [38], we anticipate that scale-up efforts could potentially result in large gains relative to the status quo. The pace of progress toward MDG 4 has stalled in South Africa [39], further underscoring the potential for perinatal depression interventions to contribute toward achieving MDG 4 goals.

STRENGTHENING THE EVIDENCE BASE

While suggestive, these estimates are not conclusive, and more work needs to be done to confirm that these potential benefits could be realized in real-world settings. As shown in **Figure 1**, both the causes of depressed mood and

Table 1 Prevalence of perinatal depression in a peri-urban settlement near Cape Town

Source	Sample and timing	Findings
Antenatal assessment		
Honikman et al., 2012 [26]	5402 women assessed during antenatal care	32% were referred to a counselor on the basis of EPDS screening and a risk factor assessment tool
Tsai et al., 2012 (personal communication)	461 women assessed during antenatal care	43% screened positive for significant depressive symptoms (EPDS≥13)
Rotheram-Borus, et al. 2011 [7,27]	1239 women assessed during second or third trimester antenatal care	42% screened positive for significant depressive symptoms (EPDS≥13)
Rochat et al., 2011 [28]	109 women assessed during antenatal care (third trimester)	47% met DSM-IV criteria for major depressive disorder
Postnatal assessment		
Tomlinson et al., 2004 [29,30]	147 women assessed at two months postnatally	35% met DSM-IV criteria for major depressive disorder (18% with onset subsequent to delivery)
Cooper et al., 2002 [31]	32 women assessed at six months postnatally	28% met DSM-IV criteria for major depressive disorder
Cooper et al., 2009 [32]	184 women assessed at six months postnatally	16% met DSM-IV criteria for major depressive disorder

the potential targets for mental health interventions can be conceptualized at several different levels [11]. Structural, psychological, and biological factors have all been shown to exert varying influences on mood [40]. Structural interventions aim to alter social structures or local contextual influences [41] that in some cases may be directly related to the MDGs. Individually targeted interventions aim to alleviate suffering that is rooted in psychological or somatic influences at the individual level, such as dysfunctional schemas or interpersonal difficulties. Mental health, in turn, influences access to and use of these bio-psycho-social resources [42], consistent with the spillover effects described in this essay.

In general, few mental health intervention studies have emphasized both mental health *and* non-mental health outcomes. Even fewer have assessed the extent to which improvements in non-mental health outcomes might be mediated by improvements in mental health [43]. For individual-level interventions, the results of randomized or econometric studies have been somewhat equivocal with regards to the spillover effects of depression treatment on MDG-related outcomes such as income generation and poverty reduction (MDG 1) [44], child health (MDG 4) [45,46], and ART adherence [47,48] and HIV acquisition risk [49] (MDG 6). Few systems-level interventions have been tested, but one recently published study showed that an innovative method of organizing the delivery of care by specialist and non-specialist health care workers can have beneficial impacts on both depression and economic productivity [50].

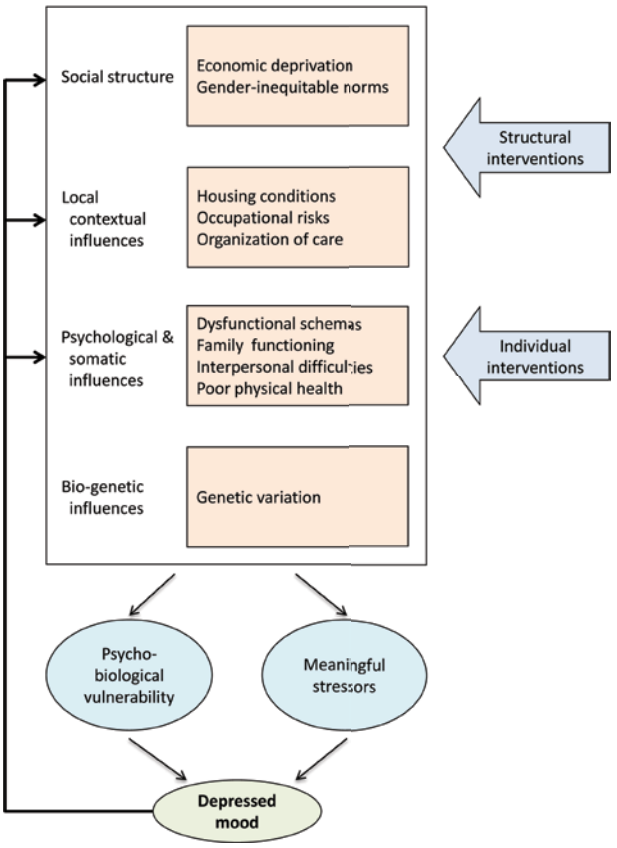


Figure 1 Conceptual framework of multilevel influences on depression and corresponding types of interventions. Adapted from McKinlay & Marceau [11].

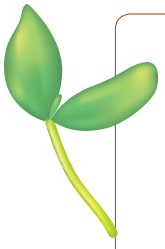
Photo: Courtesy of Dr Mark Tomlinson, personal collection

Even were the evidence base on mental health spillovers to be strengthened overnight, additional questions would need to be answered in order to determine how best to *deliver* these interventions in different contexts. Given the present lack of adequate mental health care systems financing and lack of adequate human resources for mental health in low-income countries, a scaled-up response will likely involve integration of treatment for mental disorders into primary health care settings [51]. Screening for mental disorders will need to be implemented at some level (eg, in the community, among primary health care attendees, etc.), but little evidence exists to inform programming in this area. In high-income countries, screening and case-finding interventions implemented in isolation (ie, without additional organizational enhancements) have not resulted in improved diagnostic or management outcomes [52]. Screening may potentially have benefits if integrated into wider enhanced-care programs [53,54], but few studies in low-income countries have incorporated these strategies into their design [4]. Screening instruments developed using study participants living in high-income countries will need to be adapted and validated in low-income countries [55], and separate evaluations of their test properties will be needed in order to ensure that screening yields a locally appropriate referral volume. Simply adding to the responsibilities of medical officers working within already overburdened primary health care systems is a non-starter. In order to address some of these needs, we are currently engaged in research on the use of lay health workers in community-based, perinatal care interventions [6-8,56].

CONCLUSIONS

Significant strides have been made in ensuring a greater prominence for mental health on the global agenda, reflected in the *Lancet*'s Global Mental Health series in 2007 [57] and 2011 [58], the *PLoS Medicine* Packages of Care series in 2009 [59], and the Grand Challenges in Global Mental Health initiative [60]. As of yet, however, significant commitments from global funding agencies such as the Bill and Melinda Gates Foundation have not been forthcoming. Clear priorities for mental health research in low-income countries have been identified [61]. In low-income countries, however, there are many barriers to the conduct and dissemination of mental health research [62], and there is a critical need to build organizational structures for research governance [63]. A comprehensive approach to the prevention and treatment of mental disorders would include interventions aimed at the multilevel influences on mental health and will require collaborative, interdisciplinary efforts involving both mental health and public health professionals.

In the years leading up to 2015, we hope that mental health advocacy will be intensified to ensure that programming and funding for prevention and treatment of mental disorders are not sidelined in future initiatives as they have been to date with regards to the MDGs [64] and non-communicable diseases [65]. Estimating the extent to which prevention and treatment of mental disorders potentially increase the probability of achieving indicators of political importance can capitalize on greater support for these other health goals [9,18,64]. Doing so, however, has the unattractive potential for instrumentalizing the alleviation of mental suffering and undermining concern for mental suffering for its own sake. We must not lose sight of our human development and public health priorities while also appreciating the human rights implications of taking action to mitigate one of the most common and disabling sources of human suffering worldwide.



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One in a million, or one in thousand: What is the morbidity of rabies in India?

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Rabies is the 10th biggest cause of death due to infectious diseases worldwide [1]. It is estimated that 2.5 billion people across 100 countries are at risk of contracting rabies [1]. The annual death toll is around 50 000–60 000, with 99% occurring in tropical developing countries [1]. Around 36% of these rabies related deaths occur in India every year with dog bites being responsible for 95-97% of these cases [2,3]. The annual estimated number of dog bites in India is 17.4 million, leading to estimated 18 000–20 000 cases of human rabies per year [4]. Rabies is a fatal condition with no cure, but there are preventive interventions to reduce its burden, although they are not well adopted in India. As a result, India has the largest contribution to worldwide rabies mortality [5-7]. Across Asia the annual expenditure due to rabies is estimated to be reaching 563 million USD [3].

Rabies is the 10th biggest cause of death due to infectious diseases worldwide. The annual death toll is around 50 000–60 000, with 99% occurring in tropical developing countries. Based on available evidence, a fair estimate of rabies burden in India is 2.74 rabies cases per 100 000 people annually.

Rabies typically affects the most vulnerable members of society, children and lower socio-economic classes [3]. This is likely due to poor knowledge and uptake of preventive measures. Studies have shown only around 70% of the population of India have heard of rabies, only around 30% knew to wash wounds after animal bites and a large proportion were not compliant with treatment [5]. Furthermore, rabies is not a notifiable disease in India, which makes it probable that the true burden has been underestimated [7]. Although there have been reviews focusing on rabies burden in India, the majority were published prior to 2000. They all pointed to large discrepancy between estimates of rabies burden in India, which makes it difficult for policy makers to understand the scale of the problem and plan how to tackle it. As rabies is an acute condition and its control is centered on preventive measures, incidence is the most appropriate measure of its burden in the context of improving health policy.

Over the past decade, I could only identify six studies that seemed to report the incidence of rabies in different parts of India [8-13]. I use them here to try to discuss what would be a reasonable estimate based on their reported results, but perhaps equally importantly, to expose the challenges of understanding and assessing rabies morbidity in a low-resource setting. **Table 1** shows that the case definitions used in each study were poorly reported across the board. It is also worth noting that some studies estimated the incidence of animal bites as a proxy for rabies incidence, as the latter data was not known. In order to compare estimates of rabies incidence across the 6 included studies it was necessary to first standardise all of the results. As two of the studies already reported rabies incidence as the annual number of cases per 100 000 of population, I decided to standardise all of the results to these units. All studies results were reported per year.

There was an incredible variation in the standardised measure of incidence across the studies. **Table 1** shows the standardized estimates for each study, ranging from 0.05 to 1700 rabies cases per 100 000 population. If the sample size is taken into account, then the weighted mean calcu-

Table 1 Case definitions used in studies of rabies in India in the past decade

Study title	Case definitions	Standardized estimate of annual rabies incidence and units
Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey [8]	Case definition not given. Rabies diagnosis from the records of 22 infectious diseases hospitals from all regions of the country for 1992–2002.	2 per 100 000 population
Re-evaluating the burden of rabies in Africa and Asia [9]	Case definition not given.	130 per 100 000 population
An epidemiological study of animal bites in India: results of a WHO sponsored national multi-centric rabies survey [10]	Animal bite reported in the previous year in each household surveyed. Report based on memory recall of reliable, responsible adult or available home records.	1700 per 100 000 population
A survey of hospitals managing human rabies cases in India [11]	Case definition not given. Cases were identified from medical records across 23 medical centers.	0.05 per 100 000 population
Human Rabies in Delhi [12]	Rabies diagnosis was made on the basis of exposure history and presenting clinical features.	0.88 per 100 000 population
Epidemiology of human rabies cases in Kolkata with its application to post prophylaxis [13]	Case definition not given. Rabies cases identify at Kolkata's single referral center.	3.48 per 100 000 population

lated for the 6 studies was 128.74 per 100 000 , but it was mainly affected by the 2 largest estimates of rabies incidence, as these had the second and third largest sample sizes. The simple median is 2.74 per 100 000. Unsurprisingly, the 2 most extreme values were produced from the studies that estimated the incidence of animal bites as a proxy, and did not measure the incidence of human rabies directly. As a result, those two studies are likely to greatly over estimate the incidence of rabies. If those two studies are ignored, then the mean number of annual rabies cases from the remaining 4 studies is 1.6 per 100 000 and the weighted mean is 2 per 100 000.

I propose that the median of 2.74 rabies cases per 100 000 people annually may be a fair estimate of rabies burden from the available evidence. All of the studies were retrospective cohort studies, with the exception of one prospective cohort, which is a relatively robust study design. They were all also conducted over at least a 1-year period and therefore provide a reliable estimate of annual incidence. 3 of the 6 studies contained very large study populations, including one study that contained population-wide data, leading to increased precision of the estimate. Four of the studies aimed to estimate the incidence of rabies across India and as such they used multi-centered approach across various regions. However, two of the studies focused the populations of single areas of Delhi and Kolkata, which are not likely to be demographically sim-

Photo: Courtesy of Dr David Hipgrave, personal collection

ilar or at similar risk of rabies as the Indian population as a whole. All but one of the studies recruited participants from hospitals, this biases the study as only the incidence of those attending hospital can be calculated. This may exclude those with poorer education, access to health care or those who seek traditional healing who may also be more likely to be exposed to rabies. Across all 6 studies there was potential for error and bias in the measurement of incidence particularly as none of the studies outlined strict case definitions to ensure cases of rabies were correctly identified. Also the reporting of rabies in India is known to be poor and it is likely that many cases went unreported during the study period [7]. The influence of chance was not well addressed in any of the studies with no P-values or confidence intervals reported for any of the analyses preformed. An additional source of potential bias is that 3 or the 6 identified studies were published by the same author.

Clearly, further research will be required in order to produce a better estimate of the incidence of rabies in India. This could be facilitated by making rabies a notifiable disease in order to have population-wide data of confirmed cases [14-16]. As the disease is incurable, it is important to focus policy and planning on reducing the incidence of exposure to rabies and promoting awareness and behaviors which can help to prevent the disease. It would be necessary to consult demographics of rabies exposure and barriers to treatment to best inform these changes [17]. For example vulnerable populations should be targeted. This includes those of lower socio-economic class, living in rural areas, living in areas of high human:dog density and children [18,19]. Considering some of the barriers to treatment outlined in the introduction, education is one important way of reducing rabies incidence [5]. This could include educating people about the contraction of rabies, underlining the importance of seeking treatment, advising washing animal bites with soap and water and avoiding the application of harmful traditional remedies. There is also evidence that further education is needed among doctors [20]. Other important areas to be tackled by policy are the control and vaccination of India's burgeoning dog population and encouraging the use of cell culture vaccines over sheep brain vaccines which has hopefully taken place due to the discontinuation of sheep brain vaccine by the government in 2004 [10,21].

Further research will be required in order to produce a better estimate of the incidence of rabies in India. This could be facilitated by making rabies a notifiable disease in order to have population-wide data of confirmed cases. As the disease is incurable, it is important to focus policy and planning on reducing the incidence of exposure to rabies and promoting awareness and behaviors which can help to prevent the disease.

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Setting priorities for development of emerging interventions against childhood pneumonia, meningitis and influenza

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Acute lower respiratory infections, which broadly include pneumonia and bronchiolitis, are still the leading cause of childhood mortality. ALRI contributed to 18% of all deaths in children younger than five years of age in 2008 [1], and the main pathogens responsible for high mortality were *Streptococcus pneumoniae*, *Haemophilus influenzae* and respiratory syncytial virus [2-4]. In addition, meningitis was estimated to contribute up to 200 000 deaths each year, and influenza anywhere between 25 000 and 110 000 [1,5]. It is widely acknowledged that a major portion of this mortality should be avoidable if universal coverage of all known effective interventions could be achieved. However, some evaluations of the implementation of World Health Organization's (WHO) Integrated Management of Childhood Illness (IMCI) strategy, which promotes improved access to a trained health provider who can administer "standard case management", have shown somewhat disappointing results [6-8]. Only a minority of all children with life-threatening episodes of pneumonia, meningitis and influenza in developing countries have access to trained health providers and receive appropriate treatment [6-8]. Thus, novel strategies for control of pneumonia that balance investments in scaling up of existing interventions and the development of novel approaches, technologies and ideas are clearly needed.

EMERGING INTERVENTIONS AGAINST CHILDHOOD PNEUMONIA, MENINGITIS AND INFLUENZA

Several recent studies quantified the burden of child mortality due to childhood infections [1] and sub-divided it further according to the causing infectious pathogens [2-5]. In a series of papers that followed, we systematically reviewed the available information relevant to the emerging

We conducted an expert panel exercise to assess feasibility and potential effectiveness of 29 emerging health interventions against childhood pneumonia, meningitis and influenza. 20 leading international experts from international agencies, industry, basic science and public health research took part in a CHNRI priority setting process. They used 12 different criteria relevant to successful development and implementation and showed most collective optimism towards improving low-cost pneumococcal conjugate vaccines, antibiotic pediatric formulations, the development of common-protein pneumococcal vaccines and multivalent meningococcal vaccines.

interventions against childhood pneumonia, meningitis and influenza [9-14]. We defined the list of emerging interventions of interest as follows: (i) the first set of emerging interventions was suggested by the officers from the Bill and Melinda Gates Foundation (BMGF) and it was based on strategic priorities that were being discussed at the Foundation in the year 2009; (ii) additional ideas were proposed by our team at the University of Edinburgh, after provisionally reviewing the literature on emerging interventions against childhood infections; (iii) the third set of emerging interventions was suggested by the 20 international experts invited to take part in the CHNRI expert panel meeting (see later). We eventually agreed to evaluate 29 emerging interventions that seemed feasible for reaching the implementation within a 10-year period (**Table 1**). We aimed to be inclusive and open-minded in their selection because some of them may still be far from implementation.

THE EXPERT OPINION EXERCISE

The CHNRI methodology for priority setting in health research (and technologies) investments was proposed as a systematic tool that can be used by those who develop research policy and/or invest in health research [15-18]. It should assist them to understand (i) the full spectrum of research investment options; (ii) the potential risks and benefits that can result from investments in different research options; and (iii) the likelihood of achieving reductions of persisting burden of disease and disability through investments in health research and health technologies. The CHNRI methodology has 3 stages: input from investors/policy-makers (who define the context and criteria for priority setting); input from technical experts (who propose, list in a systematic way, and then score different research investment options against a pre-defined set of criteria); and input from other stakeholders (weighing the criteria according to wider societal system of values). The method has been described in detail elsewhere and many examples of its implementation are publically available [19-22].

Table 1 The consolidated list of 29 emerging interventions against childhood pneumonia, meningitis and influenza

1	Low-cost polysaccharide conjugate vaccines for *Pneumococcus* (low-cost: US$ 3.50 per dose)
2	Low cost, cross-protective common protein vaccines for *Pneumococcus*
3	Low cost, cross-protective common protein vaccines for seasonal influenza (existing flu vaccines should be considered as a current intervention)
4	Monoclonal antibodies for passive immunization against RSV
5	Anti-RSV vaccine for use in infants
6	Anti-RSV vaccine for use in pregnant women
7	Meningitis A conjugate vaccine
8	Multivalent meningococcal vaccines
9	Combination vaccines: meningococcal + other vaccines
10	Needle-free versions of current measles vaccines
11	Heat stable versions of current measles vaccines
12	Oxygen delivery systems for low-resource settings
13	Low cost ventilatory support
14	Non-liquid pediatric antibiotic formulations for use in large scale programmes in appropriate dose
15	Vaccines against *S. aureus*
16	Passive immunization against *S. aureus*
17	Combination vaccines against multiple respiratory viruses
18	Maternal vaccination to protect neonates against neonatal sepsis: *E coli* and *Klebsiella*
19	Maternal vaccination to protect neonates against neonatal sepsis: *Streptococcus B* and *S. aureus*
20	Rapid diagnostic test for bacterial infections in children
21	Rapid multiplex assay for etiology-specific diagnosis in children
22	Rapid multiplex assay for etiology-specific diagnosis in young infants
23	Rapid diagnostic test to predict severe outcome of pneumonia episode
24	Maternal vaccination for infectious agents relevant in infants (eg, PC, Hib, influenza)
25	Effective mucosal (oral or rectal) antibiotics for neonatal infections
26	Immunomodulating agents to stimulate innate immunity
27	Surfactant replacement therapy
28	Novel interventions to reduce indoor air pollution
29	Water-free solution for hand disinfection to reduce transmission of respiratory pathogens

RSV – respiratory syncytial virus, PC – pneumococcus, Hib – *Haemophilus influenzae* Type B

The expert opinion exercise focused only on emerging interventions and a broad, long-term (downstream) context/vision. We invited 20 leading international experts from international agencies, industry, basic science and public health research to Dubrovnik, Croatia, in September 2009. The invited experts provided opinion on how the 29 chosen emerging interventions satisfy a number of criteria relevant to prioritization of support to emerging interventions against childhood infections. Based on a modified CHNRI's conceptual framework, 12 criteria for prioritization were developed for emerging interventions: (i) answerability (in an ethical way); (ii) low development cost; (iii) low product cost; (iv) low implementation cost; (v) likelihood of efficacy and effectiveness; (vi) likelihood of deliverability; (vii) likelihood of affordability; (viii) likelihood of sustainability; (ix) maximum potential impact on mortality burden reduction; (x) likelihood of acceptability to health workers; (xi) likelihood of acceptability to end users; (xii) predicted impact on equity. Further details about the modified CHNRI framework with the 12 criteria used for the expert panel meeting in Dubrovnik in 2009, and the process of the expert opinion exercise, are available from the corresponding author upon request.

The first task for the experts was to read the background information assembled about the 29 emerging interventions in a 285-page landscape review, later published as a series of papers [9-14]. The second task was to participate in the expert panel meeting where, over the course of 5 days and a total of 10 discussion sessions, the experts were told why each of the 12 criteria was chosen, and then they discussed how to apply them to each of the 29 emerging interventions. They were free to challenge all information provided to them in a background document and to share further personal knowledge or opinion with the group. Notes of their input were taken and the landscape review was being continuously amended. After each discussion session the experts were invited to score, independently of each other, all emerging interventions according to the 12 agreed CHNRI criteria. For each of the 29 emerging interventions and each criterion, each expert answered questions targeted to assess the likelihood of the proposed emerging interventions to comply with the priority-setting criterion. A summarized version of those questions is presented in **Table 2**. The full version of questionnaires that were used is available upon request from the corresponding author.

Table 2 A summarized version of questions used to assess whether proposed 29 interventions satisfy the 12 priority-setting criteria

Answerability ("1" for Yes; "0" for No; "0.5" for Undecided)
▪ Do we have a sufficient research and development capacity to make the intervention available on the market by 2020? ▪ Do we have a sufficient level of funding support to make the intervention available on the market by 2020? ▪ Would you say that it is likely that the remaining technical hurdles can be overcome to make the intervention available on the market by 2020?
Cost of Development (in US$) ("1" for Yes; "0" for N; "0.5" for Undecided)
▪ How much will it cost to get from the current stage of development to commercial availability of each emerging intervention below? a.<US$1 billion, b.<US$ 500 million, c.<US$ 100 million
Cost of Implementation (in US$) ("1" for Yes; "0" for N; "0.5" for Undecided)
▪ Is it likely to be a low-cost intervention (ie, <3.50 US$ per unit?) ▪ Can we use the existing delivery mechanisms without major modifications (eg, training, infrastructure)? ▪ Is achievement of a near-universal coverage likely to be affordable to most developing countries?
Likelihood of Efficacy (0%-100%)
▪ Please assess the likelihood (0%-100%) that adequately powered randomized controlled trials of the interventions listed below (ROWS), conducted in developing countries, would consistently show statistically significant reduction in cause-specific mortality from each of the four causes of death listed below (COLUMNS). a. Pneumonia, b. Meningitis, c. Neonatal sepsis, d. Influenza
Likelihood of Maximum Potential Impact on Disease Burden
▪ Please predict, for each of the 4 causes of death below (COLUMNS), the proportion of deaths in children under five years of age due to that cause that could be averted if the complete coverage with the emerging interventions listed below (ROWS) could be achieved? a. Pneumonia, b. Meningitis, c. Neonatal sepsis, d. Influenza
Deliverability and Sustainability ("1" for Yes; "0" for N; "0.5" for Undecided)
▪ Taking into account (i) the infrastructure and resources required to deliver emerging interventions listed below (eg, human resources, health facilities, communication and transport infrastructure); (ii) the resources likely to be available to implement the emerging interventions at the time of introduction; (iii) overall capacity of the governments (eg, adequacy of government regulation, monitoring and enforcement; governmental intersectoral coordination), and (iv) internal and external partnership required for delivery of interventions (eg, partnership with civil society and external donor agencies), would you say that the emerging interventions would be? a. Deliverable at the time of introduction, b. Affordable at the time of introduction, c. Sustainable for at least 10 y after the time of introduction Assessing Readiness of Health Systems to take Existing and Emerging Interventions to High Coverage Globally (90% Urban / 80% Rural) at this Point and at the Time of their Introduction (*"1" – we are ready (or we will be ready); "0.5" – we may be getting closer, but are not quite ready; "0" – we will not be ready;)* ▪ Please study the existing and emerging interventions against childhood pneumonia, meningitis, sepsis and influenza listed below (ROWS) and the 6 "building blocks of health systems" from the WHO framework (COLUMNS). Please indicate your assessment of the level of readiness to take each of the interventions below to high coverage globally (90% urban / 80% rural) at this point in time, and following their introduction at some future point (the latter is only needed for those interventions that are NOT already available). a. Service delivery, b. Health workforce, c. Health information systems, d. Med. products, e. Vaccines and technologies, f. Health systems financing, g. Leadership and governance
Acceptability and Equity ("1" for Yes; "0" for N; "0.5" for Undecided)
▪ Taking into account the overall context, intervention complexity, health workers' behavior and the end-user population at the time of introduction, a. Would health workers be likely to comply with implementation guidelines?, b. Would end-users be likely to fully accept the intervention?, c. Would you say that the proposed intervention has the overall potential to improve equity after 10 y following the introduction?

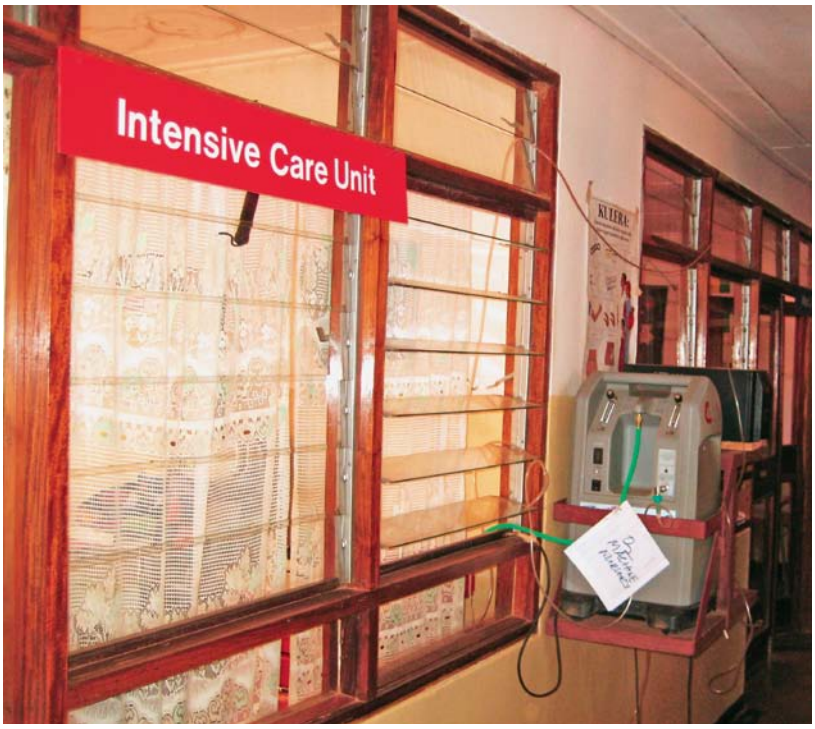


Photo: Courtesy of Alasdair Campbell, private collection

The process of expert assessment (scoring) of emerging interventions was performed as follows: all the experts answered the questionnaire related to each criterion by answering 'Yes' (1 point) or 'No' (0 points). They were also allowed to declare an informed but undecided answer (0.5 points) or declare themselves insufficiently informed to answer the question (missing input). Thus, the proposed research questions got a score from 20 experts for each of the 12 criteria. This score was "the proportion of maximum possible points scored when an answer was given" (ie, excluding the missing input), and it was a number between 0 and 100%. This number represented a direct measure of "collective optimism" of all the scorers toward each emerging intervention, given the criterion in question. Each of the 29 proposed emerging interventions received 12 criterion-specific scores, each ranging between 0%-100%. The criterion over which the experts were most uncertain was the cost of implementation, which was deemed very difficult to predict by most of them. We agreed that a separate exercise should be conducted in a low-income setting to improve understanding of the factors that affect this cost, and this has been done later [23].

The overall research priority score (RPS) for each intervention was computed as the mean value of 9 intermediate scores for 9 selected criteria. The reason why all 12 criteria weren't used is because CHNRI exercise requires that the criteria need to be relatively independent of each other (similar to principal component analysis in statistics). In this exercise, we were interested in different components of the cost (development cost, product cost, implementation cost and affordability), but those 4 criteria are in fact a single criterion, and if all 4 were kept in the exercise, this would give an undue 4-fold 'weight' to one criterion at the expense of the others. The experts agreed that the most important of the 4 cost-related criteria related to emerging interventions is 'development cost', because costs of product and implementation can be met through other mechanisms (such as GAVI, PEPFAR, Global Fund, etc.). Thus, the cost of product, cost of implementation and affordability were kept out of the final score calculation. The exact scores given to all 29 emerging interventions are presented in **Table 3**. The final report on CHNRI exercise has received the approval of the experts, among whom some (mainly from the industry) wished to remain anonymous.

THE MAIN MESSAGES

Table 3 shows that the experts declared most of their collective optimism to improvement of low-cost pneumococcal conjugate vaccines. This was followed by the development of non-liquid and mucosal antibiotic pediatric formulations with improved deliverability and acceptability in low resource settings. The development of common-protein pneumococcal vaccines and multivalent meningococcal vaccines were seen as the third most promising emerging intervention. Following this cluster at the top, the second level of priority was assigned to improvements

> The second level of priority was assigned to improvements in existing vaccines to enable needle-free delivery and heat stability, and to evaluations of maternal immunization, improved use of oxygen systems and the development of combination vaccines and vaccines against major viral pathogens. Passive immunization, action on risk factors such as indoor air pollution or poor sanitation, or development of vaccines against sepsis-causing bacterial pathogens received the lowest scores. The exercise suggested that most of the emerging interventions are still not feasible.

Table 3 The results of the CHNRI exercise: 29 emerging interventions with 9 intermediate scores and an overall research priority score

Rank	Emerging intervention	Answerability	Low development cost	Likelihood of efficacy	Max burden reduction potential	Deliverable	Sustainable	Acceptable to health workers	Acceptable to end users	Impact on equity	Research investment priority score
1	Low-cost polysaccharide conjugate vaccines for pneumococcus	0.96	0.80	0.81	0.32	0.86	0.86	1.00	0.90	1.00	**0.84**
2	Non-liquid pediatric antibiotic formulations for use in large-scale programs in appropriate dose	0.76	0.90	0.78	0.30	0.86	0.95	0.85	1.00	0.95	**0.82**
3	Low cost, cross-protective common protein vaccines for pneumococcus	0.72	0.50	0.83	0.36	0.86	0.85	1.00	0.90	1.00	**0.78**
4	New mucosal (oral and rectal) antibiotics for pneumonia and neonatal infections	0.58	0.70	0.60	0.22	0.80	0.90	1.00	0.94	0.89	**0.74**
5	Meningitis A conjugate vaccine	0.88	0.90	0.18	0.04	0.95	0.77	1.00	0.94	0.95	**0.74**
6	Multivalent meningococcal vaccines	0.75	0.70	0.17	0.07	0.95	0.77	1.00	1.00	0.95	**0.71**
7	Heat stable versions of current vaccines targeting pneumonia (eg, measles and others)	0.46	0.50	0.52	0.11	0.91	0.91	0.85	1.00	1.00	**0.69**
8	Needle-free versions of current vaccines targeting pneumonia (eg, measles and others)	0.57	0.50	0.49	0.10	0.86	0.91	0.85	0.95	0.95	**0.69**
9	Maternal vaccination for infectious agents relevant in infants (eg, PC, Hib, influenza)	0.66	0.90	0.59	0.22	0.60	0.70	0.94	0.72	0.78	**0.68**
10	Low cost, cross-protective common protein vaccines for seasonal flu (existing vaccines excluded)	0.61	0.50	0.52	0.15	0.82	0.75	0.90	0.80	0.90	**0.66**
11	Water-free solution for hand disinfection to reduce transmission of respiratory pathogens	0.88	1.00	0.69	0.18	0.65	0.50	0.67	0.56	0.67	**0.64**
12	Oxygen delivery systems for low-resource settings	0.81	1.00	0.77	0.21	0.65	0.55	0.65	0.70	0.44	**0.64**
13	Combination vaccines: meningococcal + other EPI vaccines	0.36	0.40	0.39	0.12	0.91	0.86	0.95	0.90	0.85	**0.64**
14	Vaccines against additional pathogens that cause pneumonia – multiple respiratory viruses	0.48	0.40	0.69	0.24	0.70	0.70	0.85	0.80	0.75	**0.62**
15	Anti-RSV vaccine for use in infants	0.58	0.50	0.62	0.14	0.56	0.61	0.90	0.67	0.72	**0.59**
16	Point-of-care diagnostic for bacterial infections in children	0.61	0.60	0.59	0.26	0.55	0.64	0.55	0.65	0.70	**0.57**
17	Point-of-care diagnostic for etiology-specific pathogen in young infants	0.50	0.60	0.61	0.23	0.50	0.64	0.61	0.65	0.72	**0.56**
18	Low cost ventilatory support	0.54	0.70	0.73	0.16	0.45	0.45	0.75	0.75	0.44	**0.55**
19	Anti-RSV vaccine for use in pregnant women	0.43	0.50	0.57	0.11	0.56	0.56	0.85	0.72	0.67	**0.55**
20	Vaccines against additional pathogens that cause pneumonia – *S. aureus*	0.47	0.60	0.40	0.12	0.64	0.55	0.85	0.75	0.55	**0.55**
21	Point-of-care diagnostic to distinguish viral and bacterial infections in young infants	0.36	0.60	0.61	0.20	0.50	0.64	0.61	0.65	0.72	**0.54**
22	Point-of-care diagnostic to predict severe outcome of pneumonia episode	0.29	0.40	0.63	0.32	0.41	0.59	0.67	0.85	0.72	**0.54**
23	Novel interventions to reduce indoor air pollution	0.64	0.90	0.54	0.12	0.50	0.40	0.42	0.61	0.56	**0.52**
24	Immunomodulating agents to stimulate innate immunity	0.51	0.50	0.43	0.10	0.38	0.38	0.75	0.81	0.50	**0.48**
25	Monoclonal antibodies for passive immunization against RSV	0.71	0.90	0.63	0.09	0.17	0.17	0.65	0.56	0.33	**0.47**
26	Maternal vaccination to protect neonates against major causes of neonatal sepsis – *Streptococcus B, Staphylococcus*	0.25	0.50	0.20	0.07	0.45	0.50	0.85	0.75	0.55	**0.46**
27	Surfactant replacement therapy	0.62	0.80	0.41	0.08	0.33	0.19	0.63	0.69	0.38	**0.46**
28	Maternal vaccination to protect neonates against major causes of neonatal sepsis – *E coli, Klebsiela*	0.25	0.40	0.25	0.05	0.45	0.50	0.85	0.70	0.50	**0.44**
29	Passive immunization against *Staphylococcus*	0.58	0.60	0.32	0.07	0.33	0.33	0.65	0.72	0.28	**0.43**

RSV – respiratory syncytial virus, PC – pneumococcus, Hib – *Haemophilus influenzae* Type B

in existing vaccines (eg, measles or *H. influenzae type b*) to enable needle-free delivery and heat stability. Similar overall scores were given to evaluations of maternal immunization, improved use of oxygen systems and the development of combination vaccines and vaccines against major viral pathogens. The next level of priority was assigned to various diagnostic tools, the impact of which is currently limited with sub-optimal levels of access to care, care-seeking behavior and the availability of 1st and 2nd line antibiotics. Interventions that proposed passive immunization, action on risk factors such as indoor air pollution or poor sanitation, or development of vaccines against sepsis-causing bacterial pathogens such as *S. aureus* or *E coli* received the lowest scores (**Table 3**).

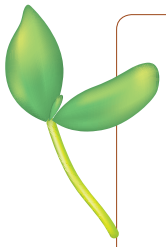
An extended version of the results of the CHNRI process with the current status of each emerging interventions' development, the key challenges that remain to be addressed, the visual representation of scores given by the expert panel to each intervention and the assessment of potential effectiveness of each intervention is available in the series of papers published elsewhere [9-14]. It should be noted that the assessment of potential effectiveness (**Table 3**) can also range from 0%-100%, but its interpretation is different than of the other 11 criteria; rather than measuring collective optimism, it actually predicts the proportion of mortality burden that could be averted through implementation.

Pneumococcal conjugate vaccines, which were treated as emerging interventions back in 2009 because of a very low uptake in low and middle income countries at the time, achieved scores over 80% for all criteria apart from "low product cost" – which indeed ended up being the main point of discussion once they were introduced. In compar-

ison, common protein pneumococcal vaccines are still held back by concerns over answerability (although it is getting closer to 80%), and over all criteria related to their future cost. Other interventions show quite different score profiles. For example, anti-RSV vaccine for use in infants failed on all criteria apart from "acceptance for health workers", whereas monoclonal antibodies for passive immunization against RSV failed entirely on product cost, affordability and sustainability concerns, although product development cost was considered feasible. The introduction of oxygen systems was considered answerable and did not suffer from major cost concerns, but these systems were not deemed sustainable, sufficiently acceptable and equitable. In comparison, common protein flu vaccines were considered sustainable, acceptable and equitable, but there were still concerns about answerability and costs of development and of the final product.

CONCLUSION

In accordance with other similar exercises with CHNRI methodology the process showed some clear advantages. The context and the criteria were transparent and the management of the process was overseen by the funding agency (BMGF) over its entire duration. This kind of partnership should result in better understanding and promote ownership and commitment to the main messages of the expert opinion exercise. The scoring process was highly systematic and structured. It was free from undue influence from prominent members within the expert group, because all the experts submitted their opinions and scores independently from each other. The varied mix of the experts from different backgrounds ensured that the scientific assessment of the research priorities is combined with a view of the broader community in which the priorities would be implemented. The entire process from the initial to the final stages was documented and can be viewed and challenged at any point in time. The final result of the process was a simple quantitative outcome ("research priority score"), which measured the "value" of each research option when all the criteria and views were taken into account. This "value" can be combined with the predicted cost of further research and development needs in order to derive an optimal mix of emerging interventions to be funded from a limited budget.



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Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010

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Background Typhoid and paratyphoid fever remain important causes of morbidity worldwide. Accurate disease burden estimates are needed to guide policy decisions and prevention and control strategies.

Methods We conducted a systematic literature review of the PubMed and Scopus databases using pre-defined criteria to identify population-based studies with typhoid fever incidence data published between 1980 and 2009. We also abstracted data from annual reports of notifiable diseases in countries with advanced surveillance systems. Typhoid and paratyphoid fever input data were grouped into regions and regional incidence and mortality rates were estimated. Incidence data were extrapolated across regions for those lacking data. Age-specific incidence rates were derived for regions where age-specific data were available. Crude and adjusted estimates of the global typhoid fever burden were calculated.

Results Twenty-five studies were identified, all of which contained incidence data on typhoid fever and 12 on paratyphoid fever. Five advanced surveillance systems contributed data on typhoid fever; 2 on paratyphoid fever. Regional typhoid fever incidence rates ranged from <0.1/100 000 in Central and Eastern Europe and Central Asia to 724.6/100 000 in Sub-Saharan Africa. Regional paratyphoid incidence rates ranged from 0.8/100 000 in North Africa/Middle East to 77.4/100 000 in Sub-Saharan Africa and South Asia. The estimated total number of typhoid fever episodes in 2010 was 13.5 million (interquartile range 9.1–17.8 million). The adjusted estimate accounting for the low sensitivity of blood cultures for isolation of the bacteria was 26.9 million (interquartile range 18.3–35.7 million) episodes. These findings are comparable to the most recent analysis of global typhoid fever morbidity, which reported crude and adjusted estimates of 10.8 million and 21.7 million typhoid fever episodes globally in 2000.

Conclusion Typhoid fever remains a significant health burden, especially in low- and middle-income countries. Despite the availability of more recent data on both enteric fevers, additional research is needed in many regions, particularly Africa, Latin America and other developing countries.

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Typhoid and paratyphoid fever remain important public health problems globally and major causes of morbidity in the developing world [1]. Typhoid and paratyphoid fever are acute and often life-threatening febrile illnesses caused by systemic infection with the bacterium *Salmonella enterica* serotype typhi and paratyphi, respectively. Classical symptoms include gradual onset of sustained fever, chills, hepatosplenomegaly and abdominal pain. In some cases, patients experience rash, nausea, anorexia, diarrhea or constipation, headache, relative bradycardia and reduced level of consciousness [2]. While both diseases share clinical features, paratyphoid fever tends to have a more benign course of illness. Without effective treatment, typhoid fever has a case-fatality rate of 10–30%. This number is reduced to 1–4% in those receiving appropriate therapy [1].

The most recent global burden of disease estimates for typhoid and paratyphoid fever reported that in 2000, there were 22 million new cases of typhoid fever, 210 000 typhoid fever-related deaths, and 5.4 million cases of paratyphoid fever [1]. This study offered improved estimates from past updates and analyses [1,3-6].

A revised estimate of the global burden of typhoid and paratyphoid fever is critically needed for developing improved strategies for disease prevention and control. The global epidemiology of these diseases has changed with global population growth and provision of clean water and sanitation systems. Advances in surveillance, improved understanding of the age distribution of the disease, and more recent studies allow for updated estimates of the global burden of typhoid and paratyphoid fever.

METHODS

Systematic review and data extraction

We conducted literature searches in PubMed and Scopus databases using combinations of the following search terms: *typhoid; Salmonella typhi; Salmonella paratyphi; incidence; prevalence; mortality; disease burden; surveillance; distribution*. The initial literature search was conducted in January 2009 and was updated on December 31, 2009. We screened study titles and abstracts focused on typhoid and/or enteric fever according to *a priori* inclusion and exclusion criteria. For papers not excluded based on title and abstract, full text articles were obtained and reevaluated for inclusion/exclusion criteria. We sought to include all studies published from 1980–2009 collecting prospective, population-based typhoid fever incidence data with blood culture confirmation of diagnosis from both active and passive surveillance studies. Intervention studies were included, but estimates were based on non-intervention groups only. Studies published in English, Spanish, Italian, Portuguese, or French were included. We excluded studies that did not diagnose typhoid fever by blood culture or that used stool culture for diagnosis. We also excluded case reports, microbiological reports, studies of carriers, and studies whose results did not allow for separation of *S. typhi* and *S. paratyphi* cases. Studies of hospitalized patients were excluded unless differentiation between inpatients and outpatients was clear; however, studies that screened for typhoid fever among individuals presenting with febrile illness at clinics/hospitals were considered separately from studies of hospitalized patients. We only included systematic review papers and excluded all commentaries. We abstracted data from the annual reports of notifiable diseases in countries with advanced surveillance systems.

Analytic methods

Because of the scarcity of information, input data for typhoid and paratyphoid fever were grouped into the 7 Super Regions as defined by the Global Burden of Disease Project (Super Region 1: Australasia, Southern Latin America, High Income North America, High Income Asia Pacific; Super Region 2: Western Europe, Eastern Europe, Central Europe, Central Asia; Super Region 3: Southern Sub-Saharan Africa, Central Sub-Saharan Africa, West Sub-Saharan Africa, East Sub-Saharan Africa; Super Region 4: Northern Africa/Middle East; Super Region 5: South Asia; Super Region 6: East Asia, South East Asia; Super Region 7: Caribbean, Andean Latin America, Central Latin America, Tropical Latin America, Oceania) [7]. We estimated the incidence using data from all eligible studies conducted within the corresponding Super Region and regional groupings. For any Super Region lacking data on paratyphoid fever, we extrapolated an incidence estimate from the Super Region with the closest typhoid fever incidence estimate.

Typhoid fever incidence rates were grouped with respect to age (ie, children <5 years and persons ≥5 years) for regions where age-specific data were available. The median proportion of typhoid fever cases observed among children <5 years of age was calculated and this figure was used to derive the estimated proportion of cases among those 5 years of age and older. We then calculated age-specific incidence rates and the annual number of typhoid fever episodes within each age strata using the median proportion of typhoid fever cases among each age group and the estimated number of overall typhoid fever episodes across all ages.

To estimate the number of typhoid fever episodes in each Super Region for 2010, we applied the median incidence for each Super Region to the corresponding population estimates. Uncertainty bounds were calculated using interquartile ranges. The total episodes were summed across Super Regions to provide the crude global typhoid fever burden and estimates of uncertainty.

An adjusted estimate of global typhoid fever burden was also calculated to account for the low sensitivity of the blood culture to isolate *S. typhi* or *S. paratyphi*. Similar to previous estimates by Crump et al., an adjustment factor of 2 was chosen based on a conservative estimate of 50% sensitivity [1]. This figure was the lowest reported sensitivity among 3 studies evaluating this culture method for typhoid fever diagnosis [8-10].

We estimated case-fatality rates for typhoid and paratyphoid fever from the published literature and the surveillance system data and applied to incidence rate estimates to calculate mortality rates.

RESULTS

The systematic review yielded 24 studies that examined typhoid fever incidence and employed blood culture as the criteria for diagnosis (**Figure 1**) [11-34]. Five advanced surveillance systems reporting blood-culture confirmed typhoid fever cases were also identified [35-39]. In addition, after the manuscript was accepted, we became aware of one recently published study that met systematic review inclusion criteria, so the analysis was updated to include this data [40]. In total, typhoid fever incidence data was abstracted from 47 countries across 14 (67%) of the 21 regions (**Table 1**). Population-based and prospective vaccine studies contributed data for 13 countries across 8 regions. The remaining incidence data was collected by typhoid fever surveillance systems in the 6 developed regions, each of which includes 1 or more countries with national-level surveillance. The developed regions include: High Income Asia Pacific, High Income North America, Central Europe, Eastern Europe, Western Europe, and Australia/New Zealand. Overall, our analysis includes national-level incidence data from 34 countries across these regions. Paratyphoid fever incidence data was available for 9 countries representing 7 (33%) of the 21 regions (**Table 2**). Only 2 regions included national-level surveillance systems reporting paratyphoid fever incidence (High Income Asia Pacific and Australia/New Zealand). Population-based studies provided paratyphoid fever data for 7 countries in 5 of the regions (Southern Latin America, North Africa/Middle East, South Asia, South East Asia, and East Asia). The median year of data collection for included studies is 2004.

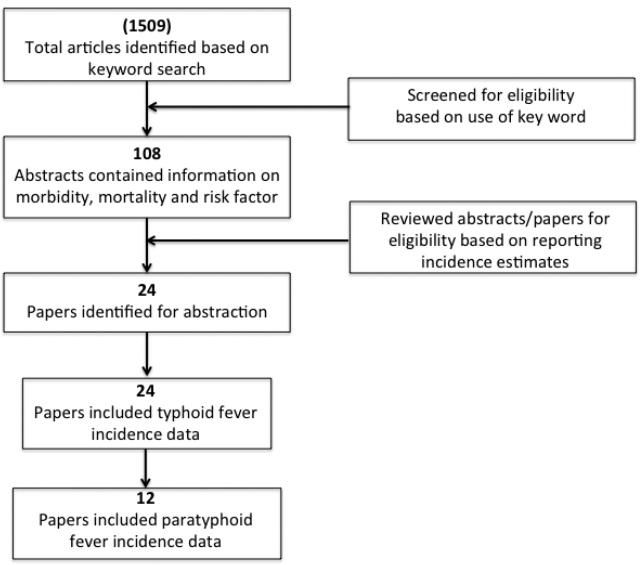


Figure 1 Selection strategy flow diagram used to identify studies on typhoid and paratyphoid fever.

Input data for typhoid and paratyphoid fever were grouped into 7 Super Regions and median incidence rates and interquartile ranges are presented in **Tables 1** and **2**, respectively. Paratyphoid fever incidence estimates were extrapolated between Super Regions on the basis of typhoid fever burden estimates. No paratyphoid fever data were available for Super Region 2 (Central Europe, Eastern Europe, Central Asia), Super Region 3 (Southern Sub-Saharan Africa, Central Sub-Saharan Africa, West Sub-Saharan Africa, East Sub-Saharan Africa), and Super Region 7 (Caribbean, Andean Latin America, Central Latin America, Tropical Latin America, Oceania). Extrapolations were made from Super Region 1 (Australia/New Zealand, Southern Latin America, High Income North America, High Income Asia Pacific, Western Europe) to Super Region 2; Super Region 5 (South Asia) to Super Region 3; and Super Region 6 (East Asia and South East Asia) to Super Region 7.

Twenty-two (88%) of the 25 eligible typhoid fever incidence studies contained age-specific typhoid fever data for children <5 years and persons ≥5 and older (**Table 3**). Age-specific data were available for 6 (29%) of 21 regions representing 5 of 7 Super Regions. All data came from low- and middle-income countries. The median proportion of typhoid fever episodes among children <5 years was 57.7%, and among persons ≥5 years, 42.3%. For Super Regions 3 and 5, the median proportion of typhoid fever cases among each age strata was used to calculate regional estimates of annual number of cases and incidence rates for each age group (**Table 4**).

The median typhoid fever incidence rate for each Super Region applied to the 2010 population estimates generates a crude global estimate of 13474369 typhoid fever episodes each year (**Table 4**). After adjusting for the low sensitivity of the blood culture typhoid test we estimate typhoid fever incidence to be 26948739 episodes annually.

There is little data to describe typhoid or paratyphoid fever case-fatality rates. In the most recent study on the global typhoid fever burden, Crump et al. assumed a case-fatality rate of 1% for typhoid fever based on hospital-based data, expert opinion, and mortality rates documented by ad-

Table 1 Input data for typhoid fever incidence rates and summarized median incidence rates by Super Region*

Super Region	Typhoid fever cases	Person-years (p-years)	Incidence (episodes/100 000 p-years)		
Super Region 1					
Australia/New Zealand [35,36]	695	17753491			3.9
	463	7731880			6.0
Latin America, Southern [11-13]	164	136525			120.1
	68	65718			103.5
	28	30906			90.6
North America, High Income [37]	7503	5250827005			0.1
Asia Pacific, High Income [38]	388	1021033000			0.0
Europe, Western [39]	31	33211134			0.1
	207	31918266			0.6
	10	3131242			0.3
	50	21861785			0.2
	35	21159333			0.2
	832	255015133			0.3
	468	328973094			0.1
	38	44771106			0.1
	51	17372910			0.3
	219	237547356			0.1
	1	1922572			0.1
	1	1636715			0.1
	192	65583388			0.3
	140	42413512			0.3
	98	179344312			0.1
	108	36600283			0.3
	1666	243565650			0.7
	4	1242390			0.3
	0	70524			0.0
	36	18857776			0.2
Median typhoid fever incidence rate per 100 000 p-years (IQR)					0.3 (0.1, 0.4)
Super Region 2					
Europe, Central [39]	0	7718750			0.0
	0	41386940			0.0
	5	40219115			0.0
	5	38157055			0.0
	17	43108829			0.0
	4	21596069			0.0
	22	8056366			0.3
Europe, Eastern [39]	6	5368443			0.1
	1	6846789			0.0
	2	10119513			0.0
Asia, Central	–	–			–
Median typhoid fever incidence rate per 100 000 p-years (IQR)					<0.1 (0, <0.1)
Super Region 3					
Sub-Saharan Africa, Southern [14]	173	20459			845.6
Sub-Saharan Africa, Central	–	–			–
Sub-Saharan Africa, West	–	–			–
Sub-Saharan Africa, East [40]	794	131550			603.6
			<5 y	**≥5 y**	**All ages**
Median typhoid fever incidence rate per 100 000 p-years (IQR)			2552.3†	366.6†	**724.6 (603.6, 845.6)**
Super Region 4					
North Africa/Middle East [15-17]	60	124590			48.2
	28	221333			12.7
	547	933333			58.7
Median typhoid fever incidence rate per 100 000 p-years (IQR)					**48.2 (12.7, 58.7)**
Super Region 5					
Asia, South [18-27]	49	12407			394.9
	63	6454			976.1
	58	27670			209.6
	129	31727			406.6
	78	19161			407.1
	122	56946			214.2
	189	41845			451.7
	32	4887			654.7
	60	15219			394.2
	78	57075			136.7
	49	29170			168.0
	80	56946			140.5
	96	37608			255.3
			<5 y	**≥5 y**	**All ages**
Median typhoid fever incidence rate per 100 000 p-years (IQR)			2104.1†	187.0†	**394.2 (209.6, 407.1)**
Super Region 6					
Asia, East [20,22,23,28]	23	104474			22.0
	5	17124			29.2
	15	97928			15.3
	15	98376			15.2
Asia, South East [20,22,23,29-32]	56	28329			197.7
	56	13538			413.6
	208	25670			810.3
	58	32164			180.3
	16	66165			24.2
	131	160261			81.7
	18	84455			21.3
	132	160257			82.4
	59	262699			22.5
Median typhoid fever incidence rate per 100 000 p-years (IQR)					29.2 (22.0, 180.3)
Super Region 7					
Caribbean	–	–			–
Latin America, Andean	–	–			–
Latin America, Central	–	–			–
Latin America, Tropical	–	–			–
Oceania [33,34]	275	1672000			16.4
	275	979781			28.1
Median typhoid fever incidence rate per 100 000 p-years (IQR)					22.3 (16.4, 28.1)

IQR – interquartile range

*Super Regions as defined by the Global Burden of Disease Project (Super Region 1: Australasia, Southern Latin America, High Income North America, High Income Asia Pacific; Super Region 2: Western Europe, Eastern Europe, Central Europe, Central Asia; Super Region 3: Southern Sub-Saharan Africa, Central Sub-Saharan Africa, West Sub-Saharan Africa, East Sub-Saharan Africa; Super Region 4: Northern Africa/Middle East; Super Region 5: South Asia; Super Region 6: East Asia, South East Asia; Super Region 7: Caribbean, Andean Latin America, Central Latin America, Tropical Latin America, Oceania) [7].

†Derived from the following data: estimated annual number of typhoid fever episodes, median proportion of cases <5 and ≥5 y of age and age-specific population estimates.

Table 2 Input data for paratyphoid fever incidence rates and summarized median incidence and mortality rates by Super Region*

Super Region	Paratyphois fever cases	Person-years	Incidence (episodes/ 100 000 p-years)	Super Region incidence (episodes/100 000 p-years)	Super Region mortality (deaths/100 000 p-years)
				Median (IQR)	Median (IQR)
Super Region 1				8.0 (0.3, 20.6)	<0.1 (0, 0.1)
Australia/New Zealand [36]	471	77 318 800	0.6		
Latin America, Southern [11,12]	21	136 525	15.4		
	17	65 718	25.9		
North America, High Income	–	–	–		
Asia Pacific, High Income [38]	219	1 021 033 000	0.0		
Europe, Western	–	–	–		
Super Region 2†				8.0 (0.3, 20.6)	<0.1 (0, 0.1)
Europe, Central	–	–	–		
Europe, Eastern	–	–	–		
Asia, Central	–	–	–		
Super Region 3†				77.4 (42.0, 130.3)	0.4 (0.2, 0.7)
Sub-Saharan Africa, Southern	–	–	–		
Sub-Saharan Africa, Central	–	–	–		
Sub-Saharan Africa, West	–	–	–		
Sub-Saharan Africa, East	–	–	–		
Super Region 4				0.8 (N/A)	<0.1 (N/A)
North Africa/Middle East [17]	7	933 333	0.8		
Super Region 5				77.4 (42.0, 130.3)	0.4 (0.2, 0.7)
Asia, South [21,23,25-27]	38	19 161	198.3		
	11	15 219	72.3		
	24	57 075	42.0		
	7	29 170	24.0		
	47	56 946	82.5		
	49	37 608	130.3		
Super Region 6				17.9 (8.8, 27.4)	0.1 (0, 0.1)
Asia, East [23,28]	5	104 475	4.8		
	27	98 376	27.4		
Asia, South East [23,29,31,32]	3	1 353 830	0.2		
	48	25 670	187.0		
	22	160 257	13.7		
	23	262 699	8.8		
Super Region 7†				17.9 (8.8, 27.4)	0.1 (0, 0.1)
Caribbean	–	–	–		
Latin America, Andean	–	–	–		
Latin America, Central	–	–	–		
Latin America, Tropical	–	–	–		
Oceania	–	–	–		

p-years – person-years, IQR – interquartile range, N/A – not applicable

*Super Regions as defined by the Global Burden of Disease Project (Super Region 1: Australasia, Southern Latin America, High Income North America, High Income Asia Pacific; Super Region 2: Western Europe, Eastern Europe, Central Europe, Central Asia; Super Region 3: Southern Sub-Saharan Africa, Central Sub-Saharan Africa, West Sub-Saharan Africa, East Sub-Saharan Africa; Super Region 4: Northern Africa/Middle East; Super Region 5: South Asia; Super Region 6: East Asia, South East Asia; Super Region 7: Caribbean, Andean Latin America, Central Latin America, Tropical Latin America, Oceania) [7].

†Extrapolation used to derive Super Region incidence estimate.

Table 3 An overview of studies with age-specific typhoid fever incidence rates by Super Regions

Super Region*	<5 y				≥5 y			
	Typhoid fever cases	Person -years	Incidence (cases/100 000 p-years)	Proportion of overall (%)	Typhoid fever cases	Person-years	Incidence (cases/100 000 p-years)	Proportion of overall (%)
Latin America, Southern [11-13]	–	–	–	–	68	65 718	103.5	N/A
	–	–	–	–	28	30 906	91.0	N/A
Sub-Saharan Africa, East [40]	240	23 167	1039.9	30.3	553	108 383	510.3	69.7
North Africa / Middle East [15-17]	9	157 631	5.8	7.6	545	775 114	70.4	92.4
Asia, South [18-27]	26	1393	1870.0	89.9	23	11 014	210.0	10.1
	28	1027	2726.4	80.9	35	5427	644.9	19.1
	11	4061	270.9	56.4	111	52 885	209.8	43.6
	58	10 118	573.2	58.1	131	31 727	412.9	41.9
	13	15 545	83.6	24.0	36	13 625	264.2	76.0
	27	2089	1292.0	86.6	69	34 543	199.7	13.4
Asia, East [20,22,23,28]	0	489	0.0	0.0	23	103 985	22.1	100.0
	–	–	–	–	15	97 928	15.3	N/A
Asia, South East [20,22,23,29-32]	26	1989	1307.0	62.9	182	23 658	769.3	37.1
	14	12 924	108.3	57.7	117	147 337	79.4	42.3
	–	–	–	–	18	84 455	21.3	N/A
Median proportion of cases split by <5 y and 5 y of age and older for low and middle income countries				57.7				42.3†

p-years – person-years, IQR – interquartile range, N/A – not applicable, y – years

*Super Regions as defined by the Global Burden of Disease Project (Super Region 1: Australasia, Southern Latin America, High Income North America, High Income Asia Pacific; Super Region 2: Western Europe, Eastern Europe, Central Europe, Central Asia; Super Region 3: Southern Sub-Saharan Africa, Central Sub-Saharan Africa, West Sub-Saharan Africa, East Sub-Saharan Africa; Super Region 4: Northern Africa/Middle East; Super Region 5: South Asia; Super Region 6: East Asia, South East Asia; Super Region 7: Caribbean, Andean Latin America, Central Latin America, Tropical Latin America, Oceania) [7].

†Derived from the median proportion of overall cases attributable to children under 5 y of age.

Table 4 Annual number of typhoid fever episodes, 2010 by Super Region*

Super Region	2010		
Super Region 1	**All ages**		
Population [41]	1 019 736 630		
Median typhoid fever incidence rate per 100 000 p-years (IQR)	0.3 (0.1, 0.4)		
Annual number of typhoid fever episodes (IQR)	3059 (1019, 4078.)		
Super Region 2	**All ages**		
Population [41]	406 303 917		
Median typhoid fever incidence rate per 100 000 p-years (IQR)	<0.1 (0, <0.1)		
Annual number of typhoid fever episodes (IQR)	406 (0, 406)		
Super Region 3	**<5 y**	**≥5years**	**All ages**
Population [41]	140 250 136	715 910 880	856 161 016
Median typhoid fever incidence rate per 100 000 p-years (IQR)	2552.3	366.6	724.6 (603.6, 845.6)
Annual number of typhoid fever episodes (IQR)	3 579 559†	2 624 183†	6 203 742 (5 167 787, 7 239 697)
Super Region 4	**All ages**		
Population [41]	4 454 87 756		
Median typhoid fever incidence rate / 100 000 p-years (IQR)	48.2 (12.7, 58.7)		
Annual number of typhoid fever episodes (IQR)	214 725 (56 576, 261 501)		
Super Region 5	**<5 y**	**≥5 y**	**All ages**
Population [41]	174 016 500	1 435 769 400	1 609 785 900
Median typhoid fever incidence rate per 100 000 p-years (IQR)	2104.1	187.0	394.2 (209.6, 407.1)
Annual number of typhoid fever episodes (IQR)	3 661 512†	2 684 263†	6 345 776 (3 374 111, 6 553 438)
Super Region 6	**All ages**		
Population [41]	2 016 815 598		
Median typhoid fever incidence rate per 100 000 p-years (IQR)	29.2 (22.0, 180.3)		
Annual number of typhoid fever episodes (IQR)	588 910 (443 699, 3 636 318)		
Super Region 7	**All ages**		
Population [41]	528 026 317		
Median typhoid fever incidence rate per 100 000 p-years (IQR)	22.3 (16.4, 28.1)		
Annual number of typhoid fever episodes (IQR)	117 749 (865 96, 148 375)		
Global Total: annual number of typhoid fever episodes (crude (IQR) / adjusted (IQR) ‡)	**13 474 369 (9 129 791, 17 843 816) / 26 948 738 (18 259 583, 35 687 632)**		

p-years – person-years, IQR – interquartile range

*Super Regions as defined by the Global Burden of Disease Project (Super Region 1: Australasia, Southern Latin America, High Income North America, High Income Asia Pacific; Super Region 2: Western Europe, Eastern Europe, Central Europe, Central Asia; Super Region 3: Southern Sub-Saharan Africa, Central Sub-Saharan Africa, West Sub-Saharan Africa, East Sub-Saharan Africa; Super Region 4: Northern Africa/Middle East; Super Region 5: South Asia; Super Region 6: East Asia, South East Asia; Super Region 7: Caribbean, Andean Latin America, Central Latin America, Tropical Latin America, Oceania) [7]

†Derived from median proportion of cases <5 and ≥5 y of age (Table 5).

‡Adjusted to account for low sensitivity of blood culture typhoid test.

vanced national surveillance systems [1]. Given we found no new data to suggest an improvement in typhoid fever case fatality rates, we also used this figure to estimate the total number of annual deaths and to derive mortality estimates, which are presented in **Table 5**. Past studies on the global paratyphoid fever burden have not reported mortality estimates. Our study assumed a case-fatality rate of 0.5% given that paratyphoid fever is generally less severe than typhoid fever [42]. Mortality estimates for paratyphoid fever are presented in **Table 2**.

DISCUSSION

Our results suggest that in 2010, there were an estimated 13.5 million typhoid fever episodes globally. This estimate is comparable to the 2000 crude estimate of 10.8 million episodes published by Crump et al [1]. We sought to update the previous estimate and in doing so, found a number of more recently published studies with higher incidence rates than those reported in older studies that influenced our final estimate. We used slightly different inclusion and exclusion criteria and applied slightly different methods for estimating incidence globally from the previous systematic review, which all contributed to the observed differences. However, given that the world's population has grown by 10% in the last 10 years, our revised estimate, compared to the previously published 2000 estimate, is well within a plausible margin of error.

Quantity of source data remains a major limitation for estimating the global burden of typhoid and paratyphoid fever. While additional data on paratyphoid fever is needed across all regions, typhoid fever estimates are limited by the scarcity of reliable incidence data from many of the developing regions in particular. Lacking surveillance systems or eligible population-based studies, typhoid fever incidence data were unavailable for 7 (33%) regions including: Central Asia, Central Sub-Saharan Africa, West Sub-Saharan Africa, Caribbean, Andean Latin America, Central Latin America, and Tropical Latin America. Furthermore, incidence estimates for several regions were based on few studies. Of note, we identified only 5 eligible studies conducted in Africa. As a result, our estimate for Super Region 3 – representing all of sub-Saharan Africa – was based on only two studies conducted in South Africa and Kenya [14,40]. Similarly, North Africa/Middle East estimates relied on only 3 studies that were carried out in Egypt [15-17]. Outside of Africa, there is also limited data available for Super Region 7. Only 2 studies from Fiji and Tonga were used to estimate the burden of disease for this region and both reported the results of pilot surveillance systems, thus there exists considerable uncertainty related to this approximation [33,34]. Additional population-based surveillance studies must be carried out in Africa and other developing regions to develop a more accurate understanding of the global typhoid fever burden.

Table 5 Summarized median typhoid fever mortality rates by Super Region*

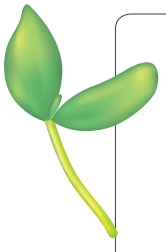
Super Region	Region	Mortality (deaths/ 100 000 p-years) [1] Median (IQR)
Super Region 1	Australia/New Zealand [35,36]	<0.1 (0, <0.1)
	Latin America, Southern [11-13]	
	North America, High Income [37]	
	Asia Pacific, High Income [38]	
	Europe, Western [39]	
Super Region 2	Europe, Central [39]	<0.1 (0, <0.1)
	Europe, Eastern [39]	
	Asia, Central	
Super Region 3	Sub-Saharan Africa, Southern [14]	7.2 (6.0, 8.5)
	Sub-Saharan Africa, Central	
	Sub-Saharan Africa, West	
	Sub-Saharan Africa, East [40]	
Super Region 4	North Africa/Middle East [15-17]	0.5 (0.1, 0.6)
Super Region 5	Asia, South [18-27]	3.9 (2.1, 4.1)
Super Region 6	Asia, East[20,22,23,28]	0.3 (0.2, 1.8)
	Asia, South East [20,22,23,29-32]	
Super Region 7	Caribbean	0.2 (0.2, 0.3)
	Latin America, Andean	
	Latin America, Central	
	Latin America, Tropical	
	Oceania [33,34]	

p-years – person-years, IQR – interquartile range
*Super Regions as defined by the Global Burden of Disease Project (Super Region 1: Australasia, Southern Latin America, High Income North America, High Income Asia Pacific; Super Region 2: Western Europe, Eastern Europe, Central Europe, Central Asia; Super Region 3: Southern Sub-Saharan Africa, Central Sub-Saharan Africa, West Sub-Saharan Africa, East Sub-Saharan Africa; Super Region 4: Northern Africa/Middle East; Super Region 5: South Asia; Super Region 6: East Asia, South East Asia; Super Region 7: Caribbean, Andean Latin America, Central Latin America, Tropical Latin America, Oceania) [7].

We restricted our analysis to studies and surveillance systems that used blood culture as the criteria for diagnosis. Although typhoid and paratyphoid fever are most commonly diagnosed using this method, it is only 50% sensitive. Factors that influence test sensitivity include antimicrobial use, the volume of blood collected, and the timing of blood collection [8,10,43]. These important limitations introduce a bias toward underestimation. In contrast, the inclusion of vaccine studies as a source for incidence data promotes a bias toward overestimation as sites are generally selected for having high incidence rates due to sample size considerations.

Typhoid and paratyphoid fever are major public health problems, especially in the developing world. Our study reports a revised estimate of the global burden of these diseases based on new data available from recent population-based studies and broader coverage of surveillance systems. In total, we identified 49 sources of new data that have become available since the 2000 estimate published by Crump et al. in 2004 [1]: 15 population-based studies, 30 national-surveillance systems, and 4 partially representative surveillance systems. Collectively, these sources provide estimates of overall typhoid fever incidence rates from 14 (67%) of the 21 regions across 5 Super Regions.

Although our understanding of the global burden of these diseases has improved with more recent data, both enteric fevers remain poorly quantified. Critical gaps in our understanding persist, as the burden remains largely unknown in many of the regions. Appreciable gains would be made by: a) developing improved diagnostic methods; b) implementing surveillance systems; and c) carrying out additional population-based research, particularly in sub-Saharan Africa and other developing countries. Recent studies have shown that paratyphoid fever accounts for an increasing proportion of enteric fever in several regions [19,23,44-47]. If this trend continues, important challenges can be anticipated in the absence of an effective vaccine for this disease. In addition, multi-drug resistant *S. typhi* and *S. paratyphi* organisms may continue to increase in prevalence and could certainly hamper efforts to reduce related morbidities. An accurate epidemiological profile of the global burden of typhoid and paratyphoid fever is important to developing effective disease prevention and control strategies.



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An estimate of syphilis incidence in Eastern Europe

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Aim Eastern Europe experienced epidemic levels of syphilis after the collapse of the Soviet Union. Presently data are less comprehensive outside the European Union (EU) and European Free Trade Association (EFTA). This review aims to identify published papers with suitable data to estimate a regional burden of disease for syphilis in the 19 member countries of Eastern Europe.

Methods A systematic literature review was conducted to identify published data relating to syphilis incidence in Eastern Europe through Web of Knowledge, PubMed and Google Scholar databases in addition to the latest surveillance report from the European Center for Disease Prevention and Control. A total of 381 papers fitted our search criteria; 30 papers were subjected to full text analysis.

Results Seven papers were included in this study and provided useable data for 13 out of 19 member countries. There was a high level of heterogeneity observed in the incidence rates from the member countries. Gross, population weighted and geographically subdivided incidence rate estimates were carried out but the comprehensiveness of some of the included data is doubtful.

Conclusions Despite the limits of the data, the incidence of syphilis in Eastern Europe is still substantially larger than that observed in the EU15 countries. This indicates that efforts to control syphilis in Eastern Europe can be enhanced; however, such goals would require significant investment in infrastructure, technology and surveillance mechanisms.

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Syphilis is a sexually transmitted disease caused by the bacterium *Treponema pallidum pallidum* [1]. If untreated the disease can cause mortality of >60% of cases, mainly due to the complications in the tertiary phase of the disease. Also important is vertical transmission, known as congenital syphilis that is associated with increased pregnancy failure rates and severe birth defects. Syphilis rates in Eastern Europe increased dramatically after the collapse of the Soviet Union (USSR), linked to changes in health infrastructure, sexual behavior and the emergence of the HIV/AIDS pandemic [2]. As a notifiable disease in Eastern Europe, syphilis is subject to

surveillance reports, however the most recent review of the topic presented data only until 2005 [2].

Globally, the incidence of syphilis is an estimated 12 million new cases annually and WHO estimates that the majority of new syphilis cases are in Southern Asia and Sub-Saharan Africa. The effects of syphilis are far reaching, as an estimated 6.2% and 9.7% of global neo-natal deaths and stillbirths respectively are caused by untreated maternal syphilis. There are several controversies regarding syphilis globally. Such as, debate of what extent men who have sex with men (MSM) and HIV infected individuals influence infection dynamics. It was recently shown that MSM had a 140 times greater prevalence than their heterosexual counterparts in New York City and a separate study reported a 77 times greater prevalence of syphilis in those infected with HIV [3]. Furthermore, as the causative agent cannot be cultured or genetically manipulated, it is unclear what, if any, drug resistance is present globally and also how HIV co-infection affects the clinical manifestations of the disease is yet unclear [1]. Within Europe, strong surveillance data are available within the European Union (EU) community, however out with the economic area surveillance is commonly on a case notification basis that has been criticized for its accuracy [2]. As such, estimating the burden of disease regionally is more problematic.

This review is aimed at estimating a regional burden of syphilis in Eastern Europe. The data extracted from the chosen papers will be standardised to achieve a mean incidence per 100 000 people per year. These rates will then be combined to provide an estimated regional burden and a population weighted regional burden of disease based on the standardised incidences of all 7 studies. As syphilis rates have previously been markedly different between countries this review will also provide an adjusted estimate based on the geographical subdivision of Eastern Europe into 4 regions to compliment the gross and weighted estimates (**Figure 1**).

Figure 1 Eastern Europe as subdivided into Northern (purple), Eastern (blue), Southern (green) and Western (red) regions, for the purposes of this review.

METHODS

Search strategy

The following databases were searched (**Figure 2**):

1) Web of Knowledge – 2000 onwards, using topic search terms "Syphilis and "Eastern Europe" or specific country name;
2) PubMed – 2000 onwards, using title/abstract search terms "Syphilis and "Eastern Europe" or specific country name;
3) Google Scholar Medical Database – 2000 onwards, using title search terms "Syphilis and "Eastern Europe" or specific country name.

Specific country name included all 19 countries included in study separated by Boolean operator 'OR'. As Google Scholar has no keyword search, a title search was performed.

Inclusion criteria

The papers resulting from our search strategy (n = 381) were first screened by title, with potentially suitable papers having their abstracts screened for any suitable data regarding syphilis (eg, new cases, incidence rates or epidemiological trends). Papers which excluded significant population demographics (eg, prison populations) or only included parts of the population (eg, blood donors, sex workers or young people) were excluded due to the inherent bias and the effect this may have on the published data were compared to the incidence for the population as a whole. Furthermore, papers only reporting epidemiological data for certain forms of the disease (eg, congenital syphilis) were also excluded as total syphilis incidence cannot be inferred from this data. Single studies or surveillance reports were treated preferentially. Reviews were analyzed and those that included appropriate data had their list of references hand-checked and, where possible, the original study was sourced for inclusion. If the original papers or reports were no longer available, or not available in English or for translation, the data presented in the review were in-

cluded, as was the case for Belarus and Turkey [4,5]. Latvian, Bulgarian, Czech, Estonian, Slovak and Slovenian data were collected from the latest EU surveillance report by the latest surveillance report from the European Center for Disease Prevention and Control (ECDC) [6]. Due to the fact that the incidence of syphilis increased from 1990 but decreased markedly in most countries until a relative stagnation in 2004–2005, data from 2005 onwards were most sought after [2]. Only a single included study pre-dates this turning point, as no other single study was available for Turkey. Where multiple studies for the same country were available, the most recent data was used and the other studies were excluded. This search strategy returned 7 papers that provided data for inclusion, representing 13 countries.

Data extraction

Data extraction from the papers differed based on the information provided. The selected papers all reported either an incidence rate per 100 000 person-years or the number of cases notified at national level across a set time period, 1–3 years for all included studies. In the event of case notifications, this data was compared with the population data available from the World Bank for the year(s) in question and this was extrapolated into an incidence rate [7]. Any study that directly reported an incidence rate had its population size analyzed using the same means and was then back transformed into a case notification rate. This allowed more accurate approximation of the sub-regional disease burden.

RESULTS

Two of the studies included in this review were periodical surveillance reports – one at national level and the other at multinational level, providing case notifications and incidence rates for each of the countries within the EU and European Free Trade Association (EFTA) [6,8]. Two reviews were also included for analysis in this review [4,5]. The Turkish study was the only available data for the country and as such just met the inclusion criteria as the data were from 2000 [5]. The Belarusian review was focused on congenital syphilis; national data for all forms was also supplied but without an original source paper that could be analyzed independently [4]. The remaining 3 included papers were case reports at a national level [9-11], which provided extractable data from which a national incidence could be inferred (**Table 1**, **2** and **3**).

The Eastern European region has a wide variance of syphilis incidence rates between its member countries based on the findings of this review (**Figure 2**). The maximum reported was 41/100 000, as reported in Belarus in 2004 [4], and the minimum observed incidence was 1.15/100 000 as reported in Albania in 2005 [9]. Thus, the ratio of these two most extreme incidences was 36:1, with a range between the values of 39.85 cases/100 000. The unweighted mean for the data was an incidence of 9.34/100 000, most similar to the situation in the Lithuania in 2009 [6]. The corresponding median value was 5.5/100 000, with the 25th and 75th percentiles for the data being 4.2 and 7.3,

Table 1 Non-standardised measures of syphilis incidence as they were reported in the studies included for analysis

Reference	Country	Disease measurement	Non-standardised value
Harxhi et al, 2010 [9]	Albania	Number of cases	37 cases
Pankratov et al. 2006 [4]	Belarus	Incidence rate	41 cases per 100 000
European Centre for Disease Control, 2011 [6]	Bulgaria	Cases and incidence rate	419 cases and 5.5 cases per 100 000
European Centre for Disease Control, 2011 [6]	Czech Republic	Cases and incidence rate	686 cases and 6.6 cases per 100 000
European Centre for Disease Control, 2011 [6]	Estonia	Cases and incidence rate	71 cases and 5.3 cases per 100 000
Ponyai et al., 2011 [10]	Hungary	Cases	2052 cases
European Centre for Disease Control, 2011 [6]	Latvia	Cases and incidence rate	223 cases and 10 cases per 100 000
European Centre for Disease Control, 2011 [6]	Lithuania	Cases and incidence rate	326 cases and 9.7 cases per 100 000
Majewski & Rudnicka, 2007 [11]	Poland	Incidence rate	2.46 cases per 100 000
Romanian Centre for prevention and control of communicable disease, 2008 [8]	Romania	Number of cases	4887 cases
European Centre for Disease Control, 2011 [6]	Slovakia	Cases and incidence rate	296 cases and 5.5 cases per 100 000
European Centre for Disease Control, 2011 [6]	Slovenia	Cases and incidence rate	47 cases and 2.3 cases per 100 000
Akturk et al., 2009 [5]	Turkey	Incidence rate	4.95 cases per 100 000

Table 2 Case definitions of syphilis cases from included studies

Country	Case definition
Albania [9]	Diagnosis of syphilis during time period leading to inclusion in national surveillance data
Belarus [4]	From review paper, case definition given only as cases of syphilis per 100 000 population
Bulgaria [6]	Diagnosis of syphilis during time period leading to inclusion in national and then EU surveillance data
Czech [6]	Diagnosis of syphilis during time period leading to inclusion in national and then EU surveillance data
Estonia [6]	Diagnosis of syphilis during time period leading to inclusion in national and then EU surveillance data
Hungary [10]	Clinician diagnosis via direct detection of pathogens, results of serological tests and clinical picture
Latvia [6]	Diagnosis of syphilis during time period leading to inclusion in national and then EU surveillance data
Lithuania [6]	Diagnosis of syphilis during time period leading to inclusion in national and then EU surveillance data
Poland [11]	Case reports referred to Public Health department
Romania [8]	Cases detected from national screening procedures
Slovakia [6]	Diagnosis of syphilis during time period leading to inclusion in national and then EU surveillance data
Slovenia [6]	Diagnosis of syphilis during time period leading to inclusion in national and then EU surveillance data
Turkey [5]	Diagnosis of syphilis during time period leading to inclusion in national surveillance data

Table 3 Summary of included studies

Country	Reference	Study type	Study time period	Study location	Incidence rate (cases/100 000)
Albania	Harxhi et al. 2010 [9]	Case reports	1997-2005	Tirana, Albania	1.2
Belarus	Pankratov et al. 2006 [4]	Review	1996-2004	Belarus (National)	41.0
Bulgaria	European Centre for Disease Control 2011 [6]	Surveillance report	2009	Bulgaria (National)	5.5
Czech	European Centre for Disease Control 2011 [6]	Surveillance report	2009	Czech (National)	6.6
Estonia	European Centre for Disease Control 2011 [6]	Surveillance report	2009	Estonia(National)	4.2
Hungary	Ponyai et al. 2010 [10]	Case reports	2005 – 2008	Department of Dermatology, Venereology, Semmelweis University	5.1
Latvia	European Centre for Disease Control 2011 [6]	Surveillance report	2009	Latvia (National)	7.3
Lithuania	European Centre for Disease Control 2011 [6]	Surveillance report	2009	Lithuania (National)	9.7
Poland	Majewski and Rudnicka 2007 [11]	Case reports	2005-2006	Warsaw, Poland (National)	2.5
Romania	Institutul de Sanatate Publica 2008 [8]	Surveillance report	2007	Romania (National)	25.7
Slovakia	European Centre for Disease Control 2011 [6]	Surveillance report	2009	Slovakia (National)	5.5
Slovenia	European Centre for Disease Control 2011 [6]	Surveillance report	2009	Slovenia (National)	2.3
Turkey	Asturk et al. 2001 [5]	Surveillance review	1991-2000	Turkey (National)	5.0

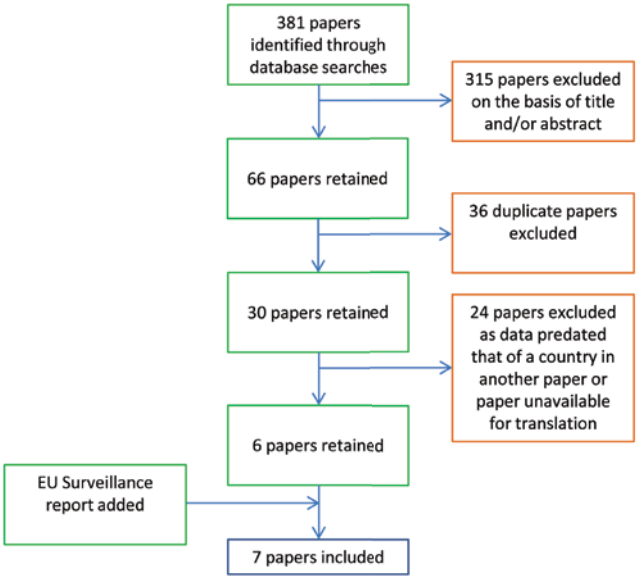


Figure 2 Search strategy.

respectively. Hence an interquartile range of 3.1 was observed. From the collective data set the estimated unweighted burden of syphilis in Eastern Europe is 9.34 new cases per 100 000 population per year (95% confidence interval (CI) 2.50–16.19), which equates to 24 073 (95% CI 6441–41710) cases in 2011, based on the 257.63 million people living in Eastern Europe at that time [7]. When the reported incidence rates were weighted against the total population at risk reported in the studies, the weighted mean for the regional burden of syphilis is 8.84 cases per 100 000 person-years (**Table 4**).

For the proposed geographically subdivided estimate, the incidence rates of the Northern, Eastern, Southern and Western regions were 7.85/100 000, 30.32/100 000, 4.85/100 000 and 3.76/100 000 person-years, respectively. Using population data to extrapolate the case notifications from this incidence data, the geographically sub-divided estimate of case notifications is 32 597 cases in 2011, giving a geographically adjusted standardised rate of 12.65/100 000 person-years.

DISCUSSION

Incidence rates have proven to be extremely heterogeneous across the 19 member states of the region, which was captured in the wide confidence interval around the unweighted mean. The geographically divided weighted mean was carried out to approach this issue. However, ideally the data for each country would be included in such an estimate, thus negating the need to estimate incidences for large countries such as the Ukraine based around the previous incidence patterns of their neighboring countries. Furthermore, the inclusion of a 95% confidence interval around the weighted mean would have been preferable.

The heterogeneity in incidence rates could also in part be due to differences in population structure. The studies only reported cases or rates for whole populations without age-group stratification. As all people are susceptible to syphilis infection the entire population are included in calculating incidence rates, it is likely that age, sex and behavior all act as confounding variables for the presented estimates [2]. Countries with an aging population or high percentage of children would likely have lower syphilis rates than a population with a greater percentage of its citizens at their sexual peak. It is well documented that birth rates have decreased in Eastern Europe since the end of the USSR and this may account for some variation in the rates between

Table 4 Summary of results*

Statistic	Value
Mean incidence	9.3/100 000 (95% CI 2.50–16.19)
Median incidence	5.5/100 000
Maximum reported incidence	41.0/100 000
Minimum reported incidence	1.2/100 000
Max/min ratio	36:1
Range	39.9
25th percentile	4.2/100 000
75th percentile	7.3/100 000
Inter-quartile range	3.1
Weighted mean incidence	8.8/100 000
Geographically adjusted weighted mean	12.7/100 000

*Incidence is expressed in person-years, with 95% confidence (CI) interval.

countries, but any further analysis of this issue was outside the scope of this review [2].

While EU surveillance data shows syphilis rates stabilizing post-2004, those countries outside the surveillance can be thought of as information gaps. One area of concern regarding data accuracy is Belarus. The country has not embraced a unified European outloo like many of its neighbors. Consequently, it is not included in the EU/EFTA surveillance data. The state of the health infrastructure is reflected in its reporting of the highest incidence rate. Belarusian syphilis rates reached their peak in 1996, with an incidence rate of 209.7 cases per 100 000 person-years, compared to between 2 and 6 cases per 100 000 in Poland, Hungary and the Czech Republic [2]. As the data included in this study is from 2004, this rate may not be representative of the true incidence rate anymore. Similar assumptions could be assigned to the estimated incidence in the Ukraine.

A suggestion for future research would be to conduct epidemiological surveillance into the incidence of syphilis in the countries of the former Soviet Union. The most recent review of syphilis in Eastern Europe stated that the incidence rate of syphilis within the Russian Federation was >50 cases per 100 000 person-years in 2005 [2]. Another review into the incidence of HIV and syphilis in Central Asian countries was carried out in 2003, returning incidence rates for 2002 of 122, 55, 12.7 and 25.8 per 100 000 person-years in Kazakhstan, Kyrgyzstan, Tajikistan and Uzbekistan, respectively [12]. Such high incidence rates are indicative that these countries experienced the same epidemics of sexually transmitted infections (STI) which followed the collapse of the Soviet Union in other countries. From this data it can be seen that the incidence rates within the former Soviet Union are generally higher than for non-Soviet Eastern European countries, although the North-Eastern European region returned incidences closer to their EU neighbors. Reasons for this may include changing demography and migration patterns within the region, eg, more young people migrating to cities to search for employment. It should be noted that the Central Asian data are now 10 years old and as syphilis rates in Eastern Europe have decreased substantially during this period, and so may have the Central Asian rates. However, this is still an avenue open to further research, as comprehensive data on the topic is sparse and analysis of trends may aid control and prevention efforts.

Of the papers retrieved from our literature search, several were regional estimates of syphilis incidence at a city or provincial level. While this review only included national estimates, it is important to note that regional studies are not always reflective of incidence rates at national level. Other studies have shown previously that syphilis rates can vary greatly within the provinces of a country [13] and the findings of this review concur with this assessment. An example of this is Czech Republic in 2009. Our literature search returned a paper that provided case notification data from a regional surveillance conducted in the Prague metropolitan area [14]. Population data for this region was sourced from the Czech Department of Statistics and the case notifications were transformed into an incidence rate for the region using this data [15]. The EU national surveillance rate and the regional rate were 6.6 and 10.8 cases per 100 000 person-years, respectively. As such, the regional estimate returned an incidence rate was 1.6 times that of the national estimate. Thus, future reviews into the burden of syphilis should be wary of including regional data as regional estimates may confound their results. A possible explanation for such a difference between the estimates is the demography of region. Prague, being the country's capital, hub of tourism and economic center may vary significantly from other regions in the density of subpopulations including men who have sex with men, sex workers and people in their sexual peak.

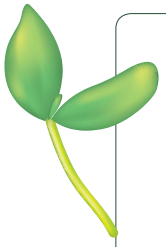
A comparison of the 2009 ECDC surveillance report data for the 5 included countries with that for 2006 shows diverging patterns in syphilis trends. It is noted by the ECDC itself that there is likely to be significant under reporting of cases and there is varying quality in the surveillance networks in each country. In Slovenia, for example, reporting is carried out by physicians with no laboratory or hospital reporting [6]. The 3 countries for which there was a large percentage increase have typically exhibited year on year increase since 2006, which cannot be attributed to either increase in syphilis incidence, or increased surveillance capability, without more in depth understanding of the development of syphilis reporting system in each country. Furthermore, there is no way to determine how accurate the reporting is for private health services. Ultimately, surveillance accuracy will be dependent on the countries health care infrastructure and as such surveillance data from the less affluent countries should be viewed with caution. When assessing the included literature as a whole, the case definitions for syphilis were not explicit for many studies. This introduces the probability of diagnostic misclassification bias, especially when considered alongside the poor access to diagnostic technology in several countries. It can be assumed that not all cases were subjected to *Treponema* testing, serology or dark field microscopy to identify the bacteria, thus diagnoses may have been made purely on clinical presentation or non-treponemal tests, many of which have well documented specificity issues [16-19]. Random misdiagnoses, while problematic, would not be as damaging to the data's validity as systematic misdiagnosis based on altered clinical presentation due to co-infection with HIV for example, which has been the subject of several other studies [16-17].

CONCLUSIONS

The incidence of syphilis in the EU 15 countries was 2.78/100 000 in 2007 [6]. When compared to our geographically subdivided estimate of 12.51/100 000 for the Eastern Europe, this highlights the great disparity in the control of sexually transmitted infections between the regions. Healthcare planning must strengthen treatment options for HIV and syphilis, as both diseases act as risk factors for each other. Reductions in HIV prevalence are likely to have a beneficial effect on syphilis prevalence and outcomes. However, syphilis infection increases chances of HIV transmission by 7 times and thus treatment can be seen as a way to reduce HIV prevalence in high risk groups [17]. Possible incentives for progress in this area are commitments to the UN Millennium Development Goals, of which HIV reduction and reducing child mortality, in this case due to congenital syphilis, are both included [17].

Investing in health infrastructure and surveillance capability would strengthen the control of syphilis. Increased knowledge of transmission dynamics would allow targeting of specific regions or subpopulations where the burden of disease is higher. One area that health policy research in Eastern Europe should address is transparency in the state of health provision and the percentage of health care provided by private services. Previous reviews have highlighted the impact of these services on STI control, but have been unable to quantify their effect [2]. Thus, this can be considered a confounder to available disease estimates including the ECDCs surveillance [6].

Current opinion suggests funding should be focused on extending the availability and efficacy of the rapid *Treponema* tests [18,19] and the extension of education programs [20]. Enhancement of the availability of rapid testing would reduce the reliance on more traditional serological and microscopy methods. Those traditional methods require transport of blood to centralised facilities and the maintenance of a "cold chain" to ensure validity of the test [19]. Furthermore, vaccine development from its current stage of testing in rabbit models should receive support, because mass vaccination campaigns have the potential to significantly to reduce the transmission potential of syphilis [19].



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PAPERS

Setting research priorities to reduce global mortality from preterm birth and low birth weight by 2015

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Aim This paper aims to identify health research priorities that could improve the rate of progress in reducing global neonatal mortality from preterm birth and low birth weight (PB/LBW), as set out in the UN's Millennium Development Goal 4.

Methods We applied the Child Health and Nutrition Research Initiative (CHNRI) methodology for setting priorities in health research investments. In the process coordinated by the World Health Organization in 2007–2008, 21 researchers with interest in child, maternal and newborn health suggested 82 research ideas that spanned across the broad spectrum of epidemiological research, health policy and systems research, improvement of existing interventions and development of new interventions. The 82 research questions were then assessed for answerability, effectiveness, deliverability, maximum potential for mortality reduction and the effect on equity using the CHNRI method.

Results The top 10 identified research priorities were dominated by health systems and policy research questions (eg, identification of LBW infants born at home within 24–48 hours of birth for additional care; approaches to improve quality of care of LBW infants in health facilities; identification of barriers to optimal home care practices including care seeking; and approaches to increase the use of antenatal corticosteriods in preterm labor and to improve access to hospital care for LBW infants). These were followed by priorities for improvement of the existing interventions (eg, early initiation of breastfeeding, including feeding mode and techniques for those unable to suckle directly from the breast; improved cord care, such as chlorhexidine application; and alternative methods to Kangaroo Mother Care (KMC) to keep LBW infants warm in community settings). The highest-ranked epidemiological question suggested improving criteria for identifying LBW infants who need to be cared for in a hospital. Among the new interventions, the greatest support was shown for the development of new simple and effective interventions for providing thermal care to LBW infants, if KMC is not acceptable to the mother.

Conclusion The context for this exercise was set within the MDG4, requiring an urgent and rapid progress in mortality reduction from low birth weight, rather than identifying long-term strategic solutions of the greatest potential. In a short-term context, the health policy and systems research to improve access and coverage by the existing interventions, coupled with further research to improve effectiveness, deliverability and acceptance of existing interventions, and epidemiological research to address the key gaps in knowledge, were all highlighted as research priorities.

The UN's Millennium Development Goal 4 (MDG4) states that childhood mortality should be reduced by two thirds between 1990 and 2015, but assessments show that the progress in mortality reduction has been disappointing in some countries [1,2]. The main reason usually proposed to explain slow progress is insufficient knowledge on how to implement existing cost-effective interventions and achieve greater coverage of these interventions in low-resource settings [3]. Generating this knowledge is a task for health research that should aim to improve efficiency, effectiveness and equity in implementation of child survival interventions in low and middle-income countries. The most recent World Health Report published by the World Health Organization (WHO) in 2012, entitled "No Health without Research", has also focused on this issue [4,5]. Through this flagship report, the WHO tried to highlight the importance of health research in reducing the burden of disease and disability in the world and "*…to provide new ideas, innovative thinking, and pragmatic advice for member states on how to strengthen their own health research systems*" [5].

To assist policy makers and donors alike in understanding the potential of different research avenues to contribute to reducing the burden of disease and disability, the Child Health and Nutrition Research Initiative (CHNRI) recently developed a methodology that allows systematic listing and transparent scoring of many competing research options, thus exposing their strengths and weaknesses [6-8]. The Department of Maternal, Newborn, Child and Adolescent Health and Development (MNCAHD) of the WHO has used this methodology to identify health research priorities to tackle five major causes of child deaths, which are thought to underlie two-thirds of all child deaths globally [9]. The most recent estimate reported 8.8 million deaths in children younger than 5 years worldwide in the year 2008, and the main causes were pneumonia (18%), diarrhea (15%), preterm birth complications (12%), neonatal infections (10%) and birth asphyxia (9%) [9]. The results of the CHNRI process coordinated by the World Health Organization to identify research priorities to reduce the mortality burden from childhood pneumonia, diarrhea, birth asphyxia and neonatal infections have already been published [10-13].

The cause "preterm birth complications", which comprises the old causes "preterm birth" and "low birth weight" (PB/LBW), is on a continuous rise as a proportional cause of child deaths globally and it may become the leading cause over the next decade, as the importance of infectious diseases steadily decreases. Currently, PB/LBW are estimated to cause around 1 million deaths each year [9]. Unfortunately, research interest and investments in preventing neonatal deaths from PB/LBW have not been commensurate with the importance of LBW as the leading child killer [14,15]. In this paper, we present the results of the CHNRI process to set research priorities to reduce the mortality burden from PB/LBW within a context and time frame of the UN's Millennium Development Goal 4.

METHODS

The CHNRI methodology for setting priorities in health research investments was proposed as a tool that could be used by those who develop research policy and/or invest in health research [6-8]. This aims to assist policy makers to understand the full spectrum of research investment options and the potential risks and benefits that can result from investments in different research. It also assesses the likelihood of achieving reductions of persisting burden of disease and disability through investments in health research. The CHNRI methodology has 4 stages: (i) input from investors/policy-makers (who define the context and the criteria for priority setting); (ii) input from a larger group of technical experts (who propose, list systematically and then independently score many research ideas); (iii) input from other stakeholders (who agree differential weights for the chosen priority-setting criteria according to wider societal system of values) [6-8;16]; and (iv) computation and discussion of the scores and analysis of the agreement between experts. The conceptual framework for the CHNRI methodology is shown in **Figure 1** and **Table 1**. More detailed explanation has been published elsewhere [6-8;16] and is also available in the Online Supplementary Document (table w1).

Input from investors/policy makers

The WHO Maternal, Newborn, Child and Adolescent Health and Development program (MNCAHD) coordinated a large international exercise in 2007-2008, involving more than 200 experts from about 80 different countries, to identify health research priorities that could directly tackle the main causes of global child mortality: pneumonia, diarrhea, birth asphyxia, preterm birth/low birth weight and neonatal infections. The aim was to inform key global donors, public investors in health research, and international agencies on research investment policies that could support efforts to accelerate the progress toward the MDG4. Thus, the context for this exercise was a short-term one, set within the MDG4 and requiring an urgent and rapid progress in mortality reduction from childhood pneumonia rather than identifying long-term strategic solutions of the greatest potential. While defining this context, the WHO also recognized the importance of context-specific issues at local or regional levels, the large problem of pneumonia morbidity, and the beneficial effects of investments in the improvement of malnutrition and other cross-cutting and cross-sectoral issues [17,18]. Further details are provided in the Online Supplementary Document (table w1).

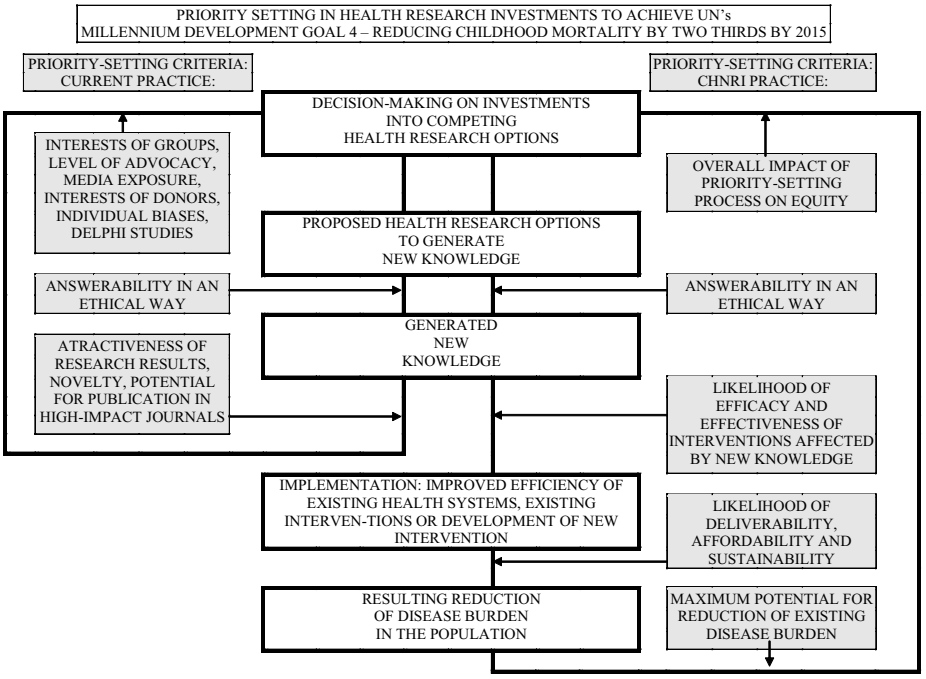

Figure 1 CHNRI's conceptual framework showing key steps required to get from investments in health research options to decrease in burden of death, disease or disability. The framework identifies criteria to discriminate between likelihoods of success of competing research options: (i) answerability; (ii) effectiveness; (iii) deliverability; (iv) maximum potential for disease burden reduction; and (v) predicted impact on equity in the population (right side). These criteria are not necessarily what drives investment decisions in health research today (left side) [6-8].

Table 1 CHNRI's starting framework from which listing of many research options (level of 3-to-5-year research program) and research questions (level of individual research papers) were being proposed by technical experts to systematically organize 82 research ideas

Research instrument	Research avenue	Research option	Research question
Epidemiological research	Measuring the burden	Technical experts were invited to use categorization of research avenues and instruments to systematically propose a number of 'research options' within each of the avenues; 'research options' correspond to the level of 3-to-5-y research program	Technical experts were invited to propose a number of very specific 'research questions', corresponding to the title of individual research papers, within each of the 'research avenues; eventually, after consolidation and removing of duplicate ideas, 82 such questions were retained for scoring
	Understanding risk factors		
	Evaluating the existing interventions		
Health policy and systems research	Studying capacity to reduce exposure to proven health risks		
	Studying capacity to deliver efficacious interventions		
Research to improve existing interventions	Research to improve deliverability		
	Research to improve affordability		
	Research to improve sustainability		
Research for development of new interventions	Basic research		
	Clinical research		
	Public health research		

Input from technical experts

Individuals with a wide range of technical expertise and regional representation were recruited to participate. A large list of research questions was drafted by the technical expert group based on recent systematic reviews and a survey of experts. Eventually, 21 researchers with interest in child, maternal and newborn health suggested 82 research ideas that spanned across the broad spectrum of epidemiological research, health policy and systems research, improvement of existing interventions and development of new interventions. They were organized using the CHNRI framework for listing research questions, shown in **Table 1**. The expert group then reviewed the questions, refining and reformulating them to allow the scoring. The final questions were sent to each technical group member for scoring. The priority-setting criteria that were adopted were: (i) answerability (in an ethical way); (ii) likelihood of effectiveness; (iii) likelihood of deliverability, affordability, and sustainability; (iv) maximum potential impact on mortality reduction; and (v) predicted impact on equity. The CHNRI framework for scoring research questions is shown in **Table 2** [7,8]. Further details are provided in the Online Supplementary Document (table w1).

Solicited input from other societal stakeholders

The five criteria for scoring (answerability, efficacy and effectiveness, deliverability, disease burden reduction and effect on equity) may be perceived to be of varying importance and the value given to each criterion may vary with the perspective of stakeholders. For example, parents who have experienced a pneumonia associated death may rate mortality reduction much higher than a research funder who may value answerability, or a health system planner who may be most concerned with deliverability. Hence, CHNRI undertook an exercise to poll a wide range of stakeholders and to weight the criteria based on values assigned by these stakeholders, as described elsewhere [16]. The weights applied in this exercise are explained in detail in the Online Supplementary Document (table w1).

Table 2 Questions answered by technical experts to assign intermediate scores for each criterion to 82 competing research ideas*

CRITERION 1: **Likelihood that research would lead to new knowledge (enabling a development / planning of an intervention) in an ethical way.**
1. Would you say the research question is well framed and endpoints are well defined?
2. Based on: (i) the level of existing research capacity in proposed research; and (ii) the size of the gap from current level of knowledge to the proposed endpoints; would you say that a study can be designed to answer the research question and to reach the proposed endpoints of the research?
3. Do you think that a study needed to answer the proposed research question would obtain ethical approval without major concerns?
CRITERION 2: **Assessment of likelihood that the intervention resulting from proposed research would be effective.**
1. Based on the best existing evidence and knowledge, would the intervention which would be developed / improved through proposed research be efficacious?
2. Based on the best existing evidence and knowledge, would the intervention which would be developed / improved through proposed research be effective?
3. If the answer to either of the previous two questions is positive, would you say that the evidence upon which these opinions are based is of high quality?
CRITERION 3: **Assessment of deliverability, affordability and sustainability of the intervention resulting from proposed research.**
1. Taking into account the level of difficulty with intervention delivery from the perspective of the intervention itself (eg, design, standardization, safety), the infrastructure required (eg, human resources, health facilities, communication and transport infrastructure) and users of the intervention (eg, need for change of attitudes or beliefs, supervision, existing demand), would you say that the endpoints of the research would be deliverable within the context of interest?
2. Taking into account the resources available to implement the intervention, would you say that the endpoints of the research would be affordable within the context of interest?
3. Taking into account government capacity and partnership requirements (eg, adequacy of government regulation, monitoring and enforcement; governmental intersectoral coordination, partnership with civil society and external donor agencies; favorable political climate to achieve high coverage), would you say that the endpoints of the research would be sustainable within the context of interest?
CRITERION 4: **Assessment of maximum potential of disease burden reduction.**
As this dimension is considered "independent" of the others, in order to score competing options fairly, their maximum potential to reduce disease burden should be assessed as potential impact fraction under an ideal scenario, ie, when the exposure to targeted disease risk is decreased to 0% or coverage of proposed intervention is increased to 100% (regardless of how realistic that scenario is at the moment – that aspect will be captured by other dimensions of priority setting process, such as deliverability, affordability and sustainability)
Non-existing interventions†
Maximum potential to reduce disease burden should be computed as "potential impact fraction" for each proposed research avenue, using the equation $PIF = [S_{(i=1 \text{ to } n)} P_i (RR_i-1)] / [S_{(i=1 \text{ to } n)} P_i (RR_i-1) + 1]$
where PIF is "potential impact fraction" to reduce disease burden through reducing risk exposure in the population from the present level to 0% or increasing coverage by an existing or new intervention from the present level to 100%; RR is the relative risk given exposure level (less than 1.0 for interventions, greater than 1.0 for risks), P is the population level of distribution of exposure, and n is the maximum exposure level.
Existing interventions‡
Maximum potential to reduce disease burden should be assessed from the results of conducted intervention trials; if no such trials were undertaken, then it should be assessed as for non-existing interventions.
Then, the following questions should be answered:
1. Taking into account the results of conducted intervention trials**, or for the new interventions the proportion of avertable burden under an ideal scenario*, would you say that the successful reaching of research endpoints would have a capacity to remove 5% of disease burden or more?
2. To remove 10% of disease burden or more?
3. To remove 15% of disease burden or more?
CRITERION 5: **Assessment of the impact of proposed health research on equity.**
1. Does the present distribution of the disease burden affect mainly the underprivileged in the population?
2. Would you say that either (i) mainly the underprivileged, or (ii) all segments of the society equally, would be the most likely to benefit from the results of the proposed research after its implementation?
3. Would you say that the proposed research has the overall potential to improve equity in disease burden distribution in the long term (eg, 10 y)?

*Possible answers: Yes = 1; No = 0; Informed but undecided answer: 0.5; Not sufficiently informed: blank
†Interventions that are in the pipeline, or could be envisaged as a possibility, but have not been licensed for implementation yet
‡Interventions that have been licensed for implementation, but may or may not have been evaluated and implemented

Computation of the research priority scores and average expert agreement

Completed worksheets were returned to the group coordinator. The overall research priority score (RPS) was computed as the mean of the scores for the five criteria [8], weighted according to the input from the stakeholders [16], according to the formula:

$$RPS = \frac{(C1 \times 0.96) + (C2 \times 0.86) + (C3 \times 0.86) + (C4 \times 1.75) + (C5 \times 0.91)}{5}$$

where C designates the scores for relevant criteria.

Average Expert Agreement (AEA) scores were also computed for each research question as the average proportion of scorers that agreed on the 15 questions asked. This is computed for each scored research investment option as:

$$AEA = \frac{1}{15} \times \sum_{q=1}^{15} \frac{\text{N of scorers who provided most frequent response}}{\text{N of all scorers}}$$

where q is a question that experts are being asked to evaluate competing research investment options, ranging from 1 to 15. For further details regarding the choice of methods, agreement statistics and interpretation see the Online Supplementary Document (table w1).

RESULTS

The scores given to all 82 research questions from individual experts are presented in Online Supplementary Document (table w2), while the final list of priorities with intermediate and final priority scores for all research questions is presented in Online Supplementary Document (table w3). In the main body of the paper, **Tables 3** and **4** show the top ten, and also the bottom-ranked ten ideas, respectively, from the 82 proposed and evaluated research questions. The latter three tables transparently present the likelihood for each research question to comply with each of the five chosen priority-setting criteria. Research questions from three broad research domains (health systems and policy research; research to improve the existing interventions; and epidemiological research) feature in the top 10 ranked research questions. The identified research priorities were dominated by health systems and policy research questions (eg, identification of LBW infants born at home within 24-48 hours of birth for additional care; approaches to improve quality of care of LBW infants in health facilities; identification of barriers to optimal home care practices including care seeking; and approaches to increase the use of antenatal corticosteriods in preterm labor and to improve access to hospital care for LBW infants). These were followed by priorities for improvement of the existing interventions (eg, early initiation of breastfeeding, including feeding mode and techniques for those unable to suckle di-

Table 3 Top 10 research questions according to their achieved research priority score (RPS), with average expert agreement (AEA) related to each question

Rank	Proposed research question	Res. type	Answerable?	Effective?	Deliverable?	Burden reduct.?	Equitable?	AEA (%)	RPS (weigh)
1	Identification of low birth weight (LBW) infants within 24-48 h of birth for additional care among those born at home	HPSR	94	89	89	71	89	82.1	84.2
2	Approaches to improve quality of care of LBW infants in health facilities	HPSR	81	100	94	79	72	80.8	83.9
3	Identification of current behaviors, and barriers and supports for optimal home care practices, including care seeking for illness	HPSR	86	78	86	74	97	77.6	82.7
4	Approaches to increase the use of antenatal corticosteriods in preterm labor in resource-poor settings	HPSR	81	91	100	71	81	81.9	82.4
5	Effective interventions for achieving early initiation of breastfeeding including feeding mode and techniques for those unable to suckle directly from the breast	RIEI	86	100	97	67	72	79.0	81.5
6	Approaches to improve access to care for the subset of LBW infants who need hospital care	HPSR	94	82	78	76	81	74.8	81.4
7	Improved criteria for identifying LBW infants who need to be cared for in a hospital	EPI	86	97	81	71	78	75.4	80.8
8	Effectiveness of improved cord care (eg, chlorhexidine application)	RIEI	94	91	81	60	86	78.7	78.8
9	Comparison of Kangaroo Mother Care (KMC) and alternative methods of keeping the LBW infant warm in community settings	RIEI	89	97	78	55	97	82.8	78.6
10	Approaches to increase the use of antibiotics for premature prolonged rupture of membranes in resource-poor settings	HPSR	94	81	75	60	97	75.7	78.2

EPI – epidemiological research, HPSR – health policy and systems research, RIEI – research to improve existing interventions, RDNI – research to develop new interventions

Table 4 The bottom 10 research questions according to their overall research priority score (RPS), with average expert agreement (AEA) related to each question

Rank	Proposed research question	Res. Type	Answerable?	Effective?	Deliverable?	Burden reduct.?	Equitable?	AEA (%)	RPS(weigh)
73	Contribution of preterm birth and intrauterine growth retardation to stunting in childhood (increased risk of LBW in next generation of girls subjected to stunting)	EPI	86	39	22	14	81	71.6	43.6
74	Development of safe and effective pharmacological methods of stimulating breastmilk supply	RDNI	64	41	34	33	42	61.8	41.5
75	Approaches to reduce smoking in fathers of unborn chidren during pregnancy	HPSR	67	25	39	21	50	63.2	37.8
76	Development of interventions for activating endogenous surfactant production through gene switching	RDNI	47	54	6	36	39	62.9	36.2
77	Investigating the relationship between sleeping arrangements, infections and SIDS in LBW infants	EPI	56	56	6	26	44	67.6	35.8
78	Determine the degree to which second-hand smoke contributes to LBW among non-smoking women	EPI	64	42	22	10	56	70.3	34.3
79	Development of methods for harmonising the composition of expressed breastmilk to infant requirements without constraining output	RDNI	50	59	13	19	42	67.1	33.9
80	Development of maternal biochemical indicators predicting low birth weight	EPI	69	28	18	26	31	63.3	33.5
81	Investigating the relationship of the home environment and neurocognitive development of LBW infants	EPI	53	50	28	0	58	71.1	31.9
82	Development of interventions for activation of HbA synthesis to ameliorate early anemia in preterm babies	RDNI	53	46	6	21	39	67.2	31.5

EPI – epidemiological research; HPSR – health policy and systems research; RIEI – research to improve existing interventions; RDNI – research to develop new interventions

rectly from the breast; improved cord care, such as chlorhexidine application; Kangaroo Mother Care (KMC) and other methods to keep LBW infants warm in community settings). The highest-ranked epidemiological question, ranked 7th, suggested improving criteria for identifying LBW infants who need to be cared for in a hospital.

The predominance of research questions from the domain of health systems and policy research is not surprising, because technical experts were asked to define research priorities that could lead to notable improvements in reduction of PB/LBW mortality by the year 2015. This short time frame benefited research questions that proposed to identify key obstacles to delivery, affordability, and sustainability of implementation of existing cost-effective interventions on a larger scale. The exercise also highlighted the value of investments that aimed to improve and optimise the use of those interventions (alone or in combination) in different contexts, and to develop entirely new approaches that could assist delivery or acceptance of the existing cost-effective interventions.

Research questions seeking to develop new interventions had only three representatives among the 30 highest-ranked questions. This is not surprising given the short specified time frame (the year 2015) by when it would be difficult to envisage new interventions that could have substantial impact, as the CHNRI exercise was conducted in 2007 and 2008. The three ideas that were still encouraged by the experts were: (i) the development of new simple and effective interventions for providing thermal care to LBW infants, if KMC is not acceptable to the mother – which was ranked at the high 12th position on the final list; (ii) identifying micronutrients whose supplementation improves functional outcomes including survival in distinct subgroups of preterm and growth retarded infants; and (iii) development of new simple and effective interventions that prevent infections and improve survival, such as new emollients for massage (see Online Supplementary Document, table w3).

Among the bottom ranked 10 research ideas, five were questions related to epidemiological research, while further four proposed the development of entirely new interventions and one was health policy and systems research question. The reasons for their low score vary substantially: the ideas on "gene switching to activate endogenous surfactant production" or "harmonising the composition of expressed breastmilk" were neither considered answerable nor equitable. The proposals to "reduce smoking in fathers of unborn children" or "develop maternal biochemical indicators predicting low birth weight" were not considered effective in mortality reduction. Interventions that should be developed from "studying sleeping arrangements, infections and SIDS", or "activation of HbA synthesis to ameliorate early anemia" were not considered deliverable in the context of low and middle-income countries. In all the cases of 10 research questions with the lowest research priority score, there was a minimal, or entirely non-existent, optimism toward their possible impact on reduction of PB/LBW within the context defined for this exercise.

The CHNRI methodology achieved very good discrimination between the 82 research questions, with the final research priority scores ranging from 84.2 (the highest-ranked research priority) to 31.5 (the lowest-ranked) out of the maximum 100. Furthermore, there was also a substantial gradient in the level of agreement among the scorers on the priority of the 82 questions, investigated by calculating "average expert agreement" (AEA). The AEA scores ranged from 0.533 to 0.828 (with the theoretical minimum of 0.250 and maximum of 1.000). AEA indicates the proportion of scorers that gave the same most frequent answer to an average question they were asked in relation to a specific research investment option. Average expert agreement values are also presented for the top and bottom 10 research questions in **Tables 3** and **4**. Generally, the questions over which the greatest level of overall agreement was observed among the experts were those that also achieved very high overall research priority scores. The greatest point of controversy was the research questions on the role of psychosocial and physical stress (such as manual labor) to preterm birth and intrauterine growth retardation (Online Supplementary Document, table w3).

DISCUSSION

Investment in global health research today would benefit from consensus regarding the context, appropriate investment strategies, and co-ordination to achieve significant reduction of the disease burden in the foreseeable future. The present exercise was designed to assist investors and policy makers in making more informed choices on their investments in health research on PB/LBW by making apparent the risks and potential benefits associated with investments in a broad spectrum of health research options. The expected "profit" from investments is associated with generating new knowledge that can be translated into development of new (or improvement of existing) interventions, which are effective, deliverable, affordable, and can reduce the existing burden of disease and disability in an equitable way. The risk is associated with research that is not likely to be answerable, or that develops products unlikely to be effective, deliverable, affordable, or sustainable by those who need them most. Investors' preference for high-risk investment in health research is particularly questionable when it is occurring in a context that requires urgent progress, such as PB/LBW mortality. The focus on complex challenges of implementation (ie, improving

health systems, training health workers including poorly educated village health workers, improving drug supply and delivery at community level, etc.), highlighted in this exercise, was reflected in many research questions being ranked near the top of the list of overall priorities.

The context for this exercise was set within the MDG4, requiring an urgent and rapid progress in mortality reduction from low birth weight, rather than identifying long-term strategic solutions of the greatest potential. In a short-term context, the health policy and systems research to improve access and coverage by the existing interventions, coupled with further research to improve effectiveness, deliverability and acceptance of existing interventions, and epidemiological research to address the key gaps in knowledge, were all highlighted as research priorities.

Although the advantages of the CHNRI methodology represent a serious attempt to deal with many issues inherent to a highly complex process of research investment priority setting, there are still concerns over the validity of the CHNRI approach and related biases. One of them is related to the fact that many possible good ideas ("research investment options") may not have been included in the initial list of research options that was scored by the experts, and to the potential bias toward items that get the greatest press. Another concern over the CHNRI process is that its end product represents a possibly biased opinion of a very limited group of involved people. In theory, a chosen group of experts can have biased views in comparison to any other potential groups of experts. Those limitations are described and discussed in greater detail in the Online Supplementary Document (table w1).

The implementation of the CHNRI methodology showed that, within the context of MDG4, a better balance should be achieved between specific domains of health research. Along with continuing strategic long-term investments in new interventions, which represent high-risk high-profit strategies, the CHNRI process suggested that more attention should be given to health policy research, health systems research, operations research, and research that addresses political, economic, social, cultural, behavioral, and infrastructure issues surrounding the problem of child mortality from PB/LBW. These domains of health research are rarely recognized as attractive by investors in health research because their results are unlikely to grab the newspaper headlines, get published in journals with high impact factors, or lead to patents and commercial products. Yet, they can generate new knowledge that can be very helpful in achieving real progress in disease burden reduction. The identified priorities are also in good agreement with the research supported by WHO's MNCAHD Department at present. They emphasize the evaluation of existing interventions and the development and testing of new delivery approaches for existing interventions. They also highlight the value of research on preventive measures, with research on new interventions being downplayed within the short-term context.

CONCLUSIONS

The context for this exercise was set within the MDG4, requiring an urgent and rapid progress in mortality reduction from PB/LBW, rather than identifying long-term strategic solutions of the greatest potential. In a short-term context, the health policy and systems research to improve access and coverage by the existing interventions, coupled with research to improve deliverability of existing cost-effective interventions in low resource contexts, and epidemiological research to address the key gaps in knowledge, were all highlighted as research priorities. These questions are mainly targeted at better understanding the barriers toward implementation, effectiveness and optimization of use of available interventions and programmes. If progress toward reduction of global PB/LBW mortality is to be improved by 2015, these are the research questions that are most likely to be of greatest importance. However, very few donors agencies recognize the importance of these domains of health research to readily invest in those options [14,15,18]. The core group of CHNRI experts made several serious attempts to influence the key donors and point to this gap and serious imbalance in health research investing between "upstream" and "downstream" health research and aims to evaluate the results of the CHNRI process conducted by the WHO at the levels of research output from academic institutions, changes in donor investment priorities, and health research policy changes at the main international organizations.

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Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality

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Objective Sepsis is a complex and hard-to-define condition with many different interactions with other disorders. Presently, there are no estimates of the burden of sepsis and septicaemia at the global level and it was not included in the initial Global Burden of Disease study. Non-maternal sepsis has only recently received attention as a substantial global public health problem. The aim of this study was to assess available data on the burden of non-maternal sepsis, severe sepsis and septic shock in the community and to identify key gaps in information needed to estimate the global burden of sepsis.

Methods Literature review of English language-based studies reporting on the incidence, prevalence, mortality or case-fatality of sepsis, severe sepsis and septic shock. The available literature was searched using the MEDLINE database of citations and abstracts of biomedical research articles published between 1980 and 2008.

Findings 8 studies reported incidence of sepsis, severe sepsis or septic shock at the national level (4 from the USA and 1 from Brazil, the UK, Norway and Australia). No studies on the incidence, prevalence, mortality or case-fatality from sepsis in developing countries were found. The population sepsis incidence ranged from 22 to 240/100 000 (most plausible estimates ranged from 149 to 240/100 000); of severe sepsis from 13 to 300/100 000 (most of the estimates were between 56 and 91/100 000); and of septic shock 11/100 000. Case-fatality rate depends on the setting and severity of disease. It can reach up to 30% for sepsis, 50% for severe sepsis and 80% for septic shock. While the data were compiled using strict inclusion and exclusion criteria, a degree of uncertainty still exists regarding the reported estimates.

Conclusion The few national-level reports available allow only a very crude estimation of the incidence of sepsis in developed countries while there is apparent lack of data from developing countries. A clear and universal definition of sepsis as well as the development of a sound epidemiological framework to begin addressing the magnitude of this problem is urgently needed through research in developing countries.

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Valid and comparable data on the population burden of diseases constitute an essential resource for guiding health policy and informing the process of resource allocation. This is particularly relevant in the developing world, where many diseases demand attention but resources are limited and budgets are tight.

The original Global Burden of Disease (GBD) study was commissioned in 1991 and conducted by the WHO in collaboration with Harvard University and others with the World Bank's funding. Its purpose was to assess the burden of 107 different diseases and injuries as well as ten risk factors for diseases in 1990 [1]. The uniqueness of the study was reflected in its use of a multitude of sources for producing the estimates and its specially designed new unit - Disability Adjusted Life Year (DALY) – for measuring the actual burden of disease. Soon following its launch, it became clear that information the prevalence and incidence of most diseases and injuries was limited, especially in developing countries [2]. The new GBD study (commenced in the spring of 2007) is the first major effort since the original GBD study was completed to carry out a complete systematic assessment of the data on all diseases and injuries and produce comprehensive and comparable estimates of the burden of diseases, injuries and risk factors for two time periods, 1990 and 2005.

Sepsis is a complex condition with many different interactions with other disorders, and because of this it can be a difficult condition to define. Several medical terms are associated with sepsis, which further complicates diagnosis and identification of the condition. Sepsis is widely defined as a systemic inflammatory response. It has three states, which develop with increased severity: sepsis is followed by severe sepsis, and finally with septic shock (see **Figure 1** for a diagram of the natural history of the sepsis syndrome and **Table 1** for different clinical and epidemiological case definitions of the sepsis syndrome). Presently there are no estimates of the burden of sepsis at the global level and it was not included in the first GBD study. Specifically, while estimates for maternal sepsis are available [5], non-maternal sepsis has only recently been receiving attention as a substantial global problem in terms of morbidity and mortality [3,6]. Sepsis is clearly a problem that has to date been neglected and underestimated by the global health community. It is primarily for this reason that sepsis has been included in the new GBD study.

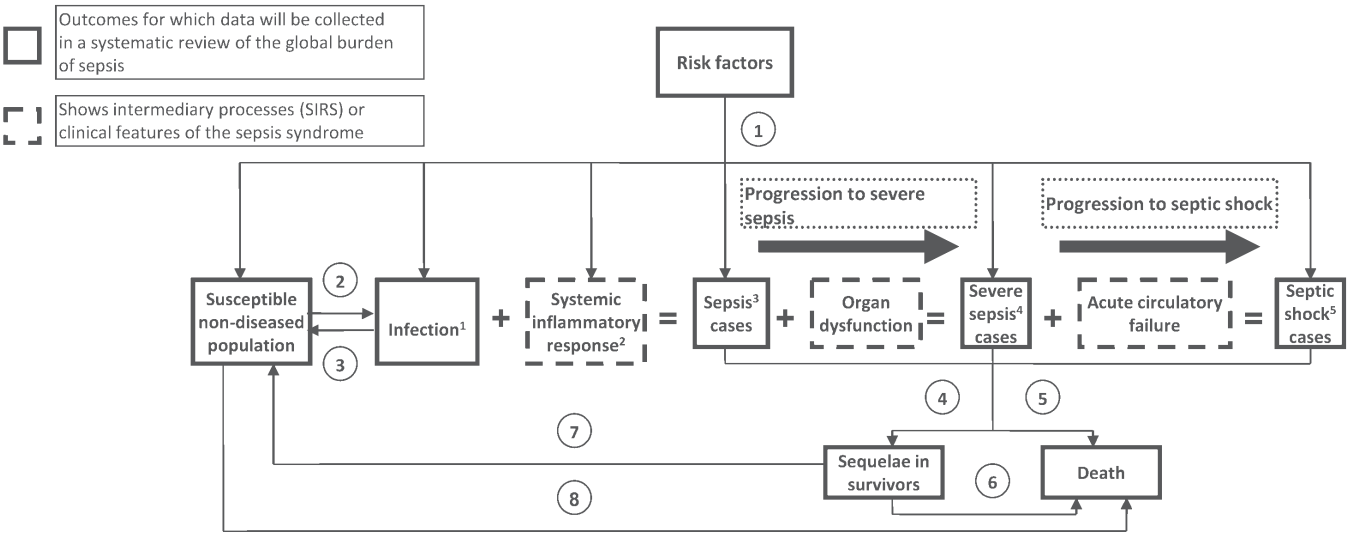


Figure 1 Natural history of sepsis diagram. Key to the diagram: 1) Potentially modifiable risk factors that increase the probability of infection, SIRS and sepsis in a non-diseased population or severe sepsis and septic shock in septic patients; 2) Incidence of sepsis: the rate at which susceptible or exposed individuals become newly affected by sepsis; 3) Remission: the rate at which individuals with sepsis stop being a sepsis case; 4) Sepsis-complication: the rate at which patients experience a complication of sepsis or start to suffer from sequelae of sepsis; 5) Case-fatality (or population mortality rate or relative risk of dying): the rate at which patients die from sepsis; 6) Complication-fatality: the rate at which patients die as a result of a complication of sepsis; 7) Individuals with sequelae who are exposed to the risk factor(s) and are susceptible to acquire infection, SIRS, sepsis, severe sepsis or septic shock again; 8) General mortality: the rate at which the population dies from any condition other than sepsis. Infection has been defined as a pathological process caused by invasion of normally sterile tissue/fluid/body cavity by pathogenic microorganisms; Systemic inflammatory response (SIRS) is a systemic inflammatory state characterized by changes in body temperature, heart rate, respiratory rate and leukocyte blood count; Sepsis is defined as confirmed or suspected infection and SIRS; Severe sepsis is defined as sepsis complicated by organ dysfunction; Septic shock in adults is defined as state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Paediatric septic shock is defined as tachycardia with signs of decreased perfusion including decreased peripheral pulses, altered alertness, and cool extremities or reduced urinary output. Hypotension occurs later than in adults and is a sign of late and decompensated shock in children [3,4].

Table 1 Clinical and epidemiological case definitions of the sepsis syndrome [3,4]

Outcome	Definition	Clinical criteria*	Epidemiological criteria	Relevant ICD-9/10 codes
Infection	Invasion of normally sterile tissue/fluid/ body cavity by microorganisms	Microbiologically confirmed or strongly suspected	*Mortality data:* Relevant ICD codes reported as underlying cause of death (primary code) on a death certificate / *Hospital episode data:* Relevant ICD codes reported as main condition on hospital episode records	*ICD-9:* 001-009, 020-027, 031, 034, 038-041, 098-099, 110-118, 130-136 / *ICD-10:* A00-A09, A20-A28, A31-A32, A39, A42-A49, A54-A64, A65-A69, A70-A74, A75-A79, A90-A99, B35-B49, B50-B64, B95-B97, B99, J00-J39, L00-L08, N39.0
Non-infective causes	Causes of SIRS that are not attributed to infectious agents	Clinically confirmed trauma, thermal injury, or sterile inflammatory processes	*Mortality data:* Relevant ICD codes reported as underlying cause of death (primary code) on a death certificate / *Hospital episode data:* Relevant ICD codes reported as main condition on hospital episode records	*ICD-9:* 574.0, 577.0, 800-904, 910-959, 996-999 / *ICD-10:* J95, K81.0, K85, S00-S99, T00-T14, T20-T32, T33-T35
Systemic inflammatory response (SIRS)	Systemic activation of the innate immune response, regardless of cause	Two or more of the following: temperature >38°C or <36°C; heart rate >90 b/min; respiratory rate >20 b/min or $Paco_2$<32 mm Hg; WBC count >12 000/ mm^3 or <4000/mm^3 or >10% band forms	*Mortality data:* Relevant ICD codes reported as any (primary or other) cause of death on a death certificate / *Hospital episode data:* Relevant ICD codes reported as main or other condition on hospital episode records	*ICD-9:* 995.90, 995.93
Sepsis	Clinical syndrome defined by the presence of both infection and SIRS	Microbiologically confirmed or strongly suspected infection and two or more of the above (see SIRS clinical criteria; this definition does not reflect the heterogeneity of causes of SIRS/ sepsis syndrome, including diverse non-infective causes)	*Mortality data:* Relevant ICD codes reported as any (primary or other) cause of death on a death certificate / *Hospital episode data:* Relevant ICD codes reported as main or other condition on hospital episode records	*ICD-9:* 003.1, 020.2, 038, 630-638, 995.91 / *ICD-10:* A02.1, A09, A22.7, A24.1, A40-A41, A54.8, B37.7, J95.0, T80.2, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5-T84.7, T85.7, T88.0
Severe sepsis	Sepsis complicated by organ dysfunction	Sepsis and organ dysfunction, hypoperfusion or hypotension; hypoperfusion may include: lactic acidosis or oliguria or acute alteration in mental status	*Mortality data:* Relevant ICD codes reported as any (primary or other) cause of death on a death certificate / *Hospital episode data:* Relevant ICD codes reported as main or other condition on hospital episode records	*ICD-9:* 276.2, 286.2, 286.6, 286.9, 287.3-287.5, 293, 348.1, 384.3, 357.82, 359.81, 458.0, 458.8, 458.9, 518.81, 518.82, 518.85, 570, 572.2, 572.3, 580, 584.5-584.9, 585, 780.01, 780.09, 785.5, 785.51, 785.59, 786.09, 796.3, 799.1, 995.92, 995.94 / *ICD-10:* D65, E87.2, G93.4, I.95, I95.1, J96.0, K72, N17, R57.0, T80.2
Septic shock	Circulatory failure characterized by arterial hypotension unexplained by other causes	Sepsis induced hypotension (systolic blood pressure <90 mm Hg or a reduction of ≥40 mm Hg from baseline) despite adequate fluid resuscitation	*Mortality data:* Relevant ICD codes reported as any (primary or other) cause of death on a death certificate / *Hospital episode data:* Relevant ICD codes reported as main or other condition on hospital episode records	*ICD-9:* 009.0, 415.12, 449, 639.5, 785.51, 785.52, 998.0 / *ICD-10:* A41.9, R57.0, T80.2

Producing estimates for the global burden of sepsis as part of the wider GBD study is a complex multi-stage process. The aim of the present study is to determine and evaluate the available information on the burden of sepsis in the community and to identify key gaps in information needed to estimate the global burden of sepsis. This research constitutes a preliminary step in understanding the availability of data on the burden of sepsis and will contribute, alongside other research, to the discussion surrounding whether or not it is possible to assess the global burden of sepsis. The specific objectives of the study are: (i) to undertake a systematic review of the available English language-based literature on the incidence, prevalence and mortality of sepsis, severe sepsis and septic shock; (ii) to apply clear inclusion and exclusion criteria to the data and tabulate the extracted results; (iii) to comment on the quality and spread of data found; and (iv) to discuss the potential future use of this review's findings and how the results can be further developed.

METHODS

Figure 2 outlines the research plan that was followed. The literature review was performed by undertaking free text searches in the title and abstract fields of the Medline database for all human studies from 01/01/1980 to 28/02/2008. The following broad search terms were used: 'sepsis', 'septicaemia'/'septicaemia', 'incidence', 'prevalence', 'morbidity', mortality', 'etiology'/'etiology' and 'risk factors'. Both the American and English spellings were used to ensure

searches were thorough. The terms sepsis and septicaemia are used interchangeably in the academic literature [7], so both were included in the search and by truncating the word sepsis the search also included studies reviewing septic shock and severe sepsis.

The search also included the terms etiology and risk factors (see above) and while these have no relevance to this study they were included with the wider GBD study in mind. This study provides an opportunity to review this additional data for use in future research on the topic of sepsis. Going through these search results also gives a richer understanding of the subject matter and the pool of information available about sepsis. To ensure the focus on the chosen outcomes, the search term specified that an estimate for incidence, prevalence, mortality or morbidity was included. The initial 13 848 results had their titles reviewed to narrow the number of studies down to those most useful to achieve the aims. The initial screening retained all studies that were relevant to incidence, prevalence, case-fatality, mortality or morbidity, and those that reported any numerical rates in their abstracts as well as any studies that were relevant to the GBD exercise. This resulted in 182 abstracts. This initial filter was very broad to ensure that no potentially useful results were missed and the maximum number of studies possible could enter the next stage of the review.

In the second round of screening, the 182 retained entries were reviewed for reporting a specific figure for incidence, prevalence, mortality or morbidity, which was obtained from their original data, OR whether they were community based studies. At this stage only articles that had their own original data were included. This was done to ensure that methodology behind the estimates reported could be assessed and that the quality of the study could be reviewed. All community studies were included as these are the most helpful type of studies for later projections of the burden to the larger population. At this point the 77 studies that were relevant to the GBD study were separated from the remaining results so as to ensure they were not included in the final filter. For the remaining accepted 100 references, full articles were obtained and reviewed to see if they fulfilled the inclusion criteria or were subject to exclusion criteria (explained in **Figure 2**).

At the final stage there were 12 articles remaining for abstraction from the first reviewer and 16 from the second reviewer, with 8 of them overlapping and further 10 retained after deliberation process (**Figure 2**). The criteria during selection and deliberation were intended to be in-

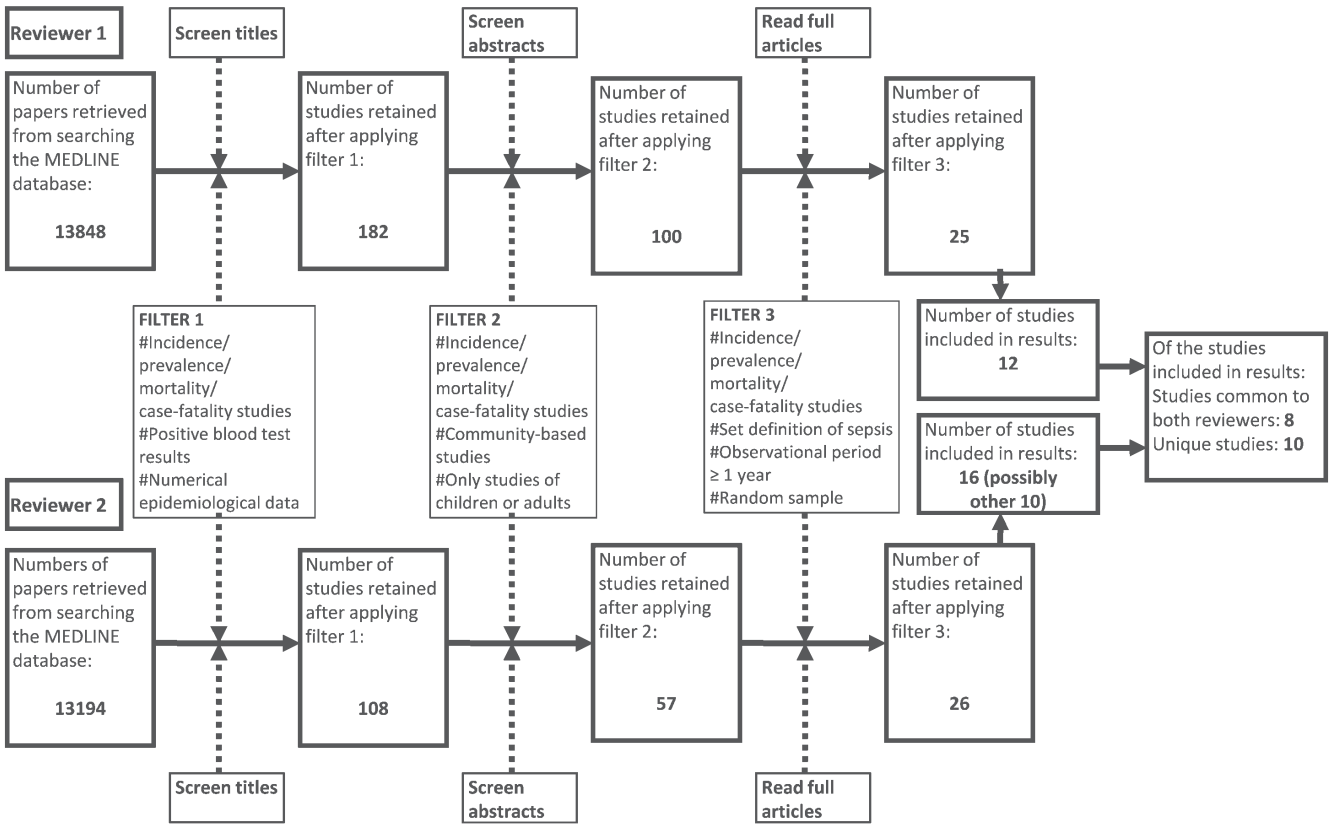


Figure 2 Results from the literature review of the global burden (incidence, prevalence and mortality/case-fatality) of sepsis.

clusive but also ensure only good quality studies were included. The requirement for estimates to be from within the date range of 1980 – 2008 was enforced to ensure that the numbers reported were still relevant. The studies had to span at least 12 months to ensure that seasonal variations did not affect the results. The requirement for an acceptable definition of sepsis in the articles was important to ensure that all the studies complied with the ACCP or ICD code definitions of sepsis that were highlighted at the start of this investigation.

Studies that looked at specific population or sepsis as a secondary condition were not included as these cannot be generalized to the whole population. Neonatal and maternal sepsis studies were not included because these are regarded as separate conditions in the ICD classification system.

RESULTS

The few national-level reports available presented a very broad range of estimates for the incidence of sepsis in different countries. The three available estimates of the incidence of sepsis in the USA, all of which were based on hospital records, ranged from 500 000 [8] to 660 000 cases per year [9]. This roughly translates into an incidence of 300 per 100 000 [10], and represents the most reliable estimate representative of the industrialized countries.

Some of the directly reported estimates of the incidence of sepsis from the smaller regions of Europe include 2007 estimate of 61 per 100 000 person-years in Valencia, Spain [11]; then about 123 per 100 000 per year incidence for hospital admissions due to sepsis in 2006 in France [4], some 38 cases per 100 000 in the adult population in Norway [12] and 149 cases per 100 000 in Finland in 1999 [13].

Much fewer studies are available for the developing world, and the etiological spectrum in low and middle-income countries is likely to be very different from the industrialized ones. Therefore, the burden of sepsis in those parts of the world appears to remain uncharacterized. **Table 2** present the characteristics of identified studies of the incidence, prevalence and mortality rate of sepsis at the population level. All the studies reported their own original results based on hospital findings with a clearly defined credible population denominator which in some cases has been used to produce the national estimates that the studies reported [9,10,13-25].

The search revealed only 8 studies that reported incidence of sepsis, severe sepsis or septic shock at the national level (4 from the USA and 1 each from Brazil, the UK, Norway and Australia) **(Table 2)**. Over the period 1980-2008, there appeared to be no studies that assessed incidence, prevalence, mortality or morbidity from sepsis in low-income countries. Reported incidence of sepsis at the population level ranged from 22 to 240/100 000 (although the most plausible estimates were between 149 and 240/100 000); of severe sepsis from 13 to 300/100 000 (although most of the estimates were between 56 and 91/100 000); and of septic shock 11/100 000. Mortality rates depend on the setting and severity of disease. It can reach up to 30% for sepsis, 50% for severe sepsis and 80% for septic shock.

Although the available information is still far from sufficient to understand thoroughly the magnitude of the global burden of sepsis, studies convincingly show that sepsis is a significant health problem even in developed countries. We can deduce that more than 1 in 1000 people in developed countries develop sepsis each year, and between a third and a half of them progress to severe sepsis. Because sepsis is most frequently affecting those most vulnerable (infants, young children and very old and ailing patients), the mortality rate is quite high, even at hospitals: it is about 10% for children, but much higher in the elderly, where it ranges between 15% and 80%, depending on the severity of sepsis and the rate of progression toward septic shock.

Those are the only general conclusions that one can reliably draw from the available literature. The few national-level reports available allow only a very crude estimation of the incidence of sepsis in developed countries. However, there is no information on developing countries. Specific definitions of the problem of sepsis and a sound epidemiological framework to begin addressing the magnitude of this problem are urgently needed through research in developing countries.

DISCUSSION

The purpose of the GBD study is to quantify measures of what the burden of disease is on a national and international scale in a form that is comprehensive and beneficial for the public health community. The present study can be considered as a preliminary step in an attempt to quantify the disease burden of sepsis, by assessing the availability of data and highlighting any gaps in existing data.

The definition of sepsis, severe sepsis and septic shock in available studies

A thorough inspection of studies highlights an almost completely consistent definition of sepsis that was concordant with that of the American College of Chest Physicians (ACCP)'s definition (1992) and the ICD codes (version 9) [26]. The ACCP's definition appears to be the most highly regarded and in several studies the inclusion criteria was simply that they complied with the aforementioned definition [26]. Several studies also referred to the ICD codes as their means of identifying sepsis patients [26]. However,

Table 2 Identified studies of the incidence, prevalence and mortality from sepsis

Article	Country studied	Geographic setting	Population studied	Time setting and duration	Incidence as reported (prevalence only where indicated)	Mortality as reported
Martin et al. [9]	United States	Nationwide	750 million hospitalizations in the United States, identified 10319418 cases of sepsis	22-year period	240.4 per 100000 population	17.9% (1995-2000)
Silva et al. [14]	Brazil	Five mixed ICUs in two different regions of Brazil: São Paulo State and Santa Catarina State	The total number of enrolled patients was 1383 (81.9%) out of 1688 patients admitted to the ICUs of the participating centers.	21 May 2001 – 31 January 2002	*Sepsis:* 61.4 per 1000 patient-days / *Severe sepsis:* 35.6 per 1000 patient-days / *Septic shock:* 30.0 per 1000 patient-days	*Sepsis:* 33.9% / *Severe sepsis:* 46.9% / *Septic shock:* 52.2%
Elhag et al. [15]	Kuwait	Jabriya, Kuwait City – Mubarak AI-Kabeer Teaching Hospital	3845 patients / 19606 patients	18 months (January 1982 – June 1983)	10.9/1000 hospital admissions	
Flaatten et al. [13]	Norway	Nationwide	All patients admitted to all Norwegian hospitals during 1999	One year	*National:* 1.49 cases/1000 inhabitants / *Under 1:* 1.1/1000 / *Over 80:* 8.7/1000	13.5%
Hoa et al. [16]	Vietnam	Ho Chi Minh City – southern Viet Nam.	All patients admitted to the hospital whose blood culture was positive	1 June 1993 – 30 May 1994	20.4 episodes per 1000 admissions	6.0%
Harrison et al. [17]	United Kingdom	Nationwide	343860 admissions to 172 adult units	December 1995 – January 2005	Severe sepsis: 66 hospital admissions per 100000 population	
Angus et al. [10]	USA	Florida, Maryland, Massachusetts, New Jersey, New York, Virginia and Washington.	All acute care hospitalizations with ICD-9-CM codes for both a bacterial or fungal infectious process	1995 (12 months)	3.0 cases per 1000 population	*Severe sepsis:* 28.6%
Braun et al. [18]	USA	Midwest, Northeast, Southeast, and Western United States	Enrollees in 16 IPA network plans	1 July 1995 – 31 December 1999	Severe sepsis: 0.91 cases of per 1000 enrollees	
Finfer et al. [19]	Australia and New Zealand	Twenty-three closed multi-disciplinary ICUs of 21 hospitals (16 tertiary and 5 University affiliated) in Australia and New Zealand	Results are presented for 3543 ICU admissions in 3338 patients	1999 – 2000	0.77 per 1000 population	
Engel et al. [20]	Germany	Random sample of German hospitals in all 16 federal states of Germany and belonging to 310 hospitals	1380 hospitals (total number of beds: 488727)		*Sepsis prevalence:* 12.4% / *Severe sepsis prevalence:* 11.0%	
Salvo et al. [21]	Italy	99 Italian ICUs, distributed throughout the country	1101 patients who fit criteria from all the ICUs	April 1993 – March 1994		*Sepsis:* 36.0% / *Severe sepsis:* 52.0% / *Septic shock:* 81.8%
Watson et al. [22]	USA	Florida, Maryland, Massachusetts, New Jersey, New York, Virginia and Washington	942 non-federal hospital admissions under 19 y olds.	1995 (12 months)	*Severe sepsis:* 0.56 cases per 1000 children / *Severe sepsis, infants (<1 y):* 5.16 per 1000 / *Severe sepsis, 1–4 y:* 0.49 per 1000 / *Severe sepsis, 5–9 y:* 0.22 per 1000 / *Severe sepsis, 10-14 y:* 0.20 per 1000 / *Severe sepsis, 15–19 y:* 0.37 per 1000	

ICU – intensive care unit, y – year

variations in the studies' definitions of sepsis were only seen in the Latin American studies highlighted by the Jaimes' (2005) review [27]. The articles deemed all cases where there had been confirmation of bacteremia to be equivalent to a positive diagnosis of septicaemia. This does not comply with the ICD codes or the ACCP's criteria. In all the studies cases were only included when positive blood cultures had confirmed the presence of bacteria. It was also clearly highlighted whether the study was looking at sepsis, septic shock or severe sepsis and no study combined the three states.

Study populations and outcomes in available epidemiological studies of the burden of sepsis

Only a limited number of studies examined sepsis or its subsequent states in isolation. Much of the research focused on the epidemiology of sepsis in specific high-risk populations. The majority of available studies assessed post-operative sepsis incidence and burn related sepsis both of which are irrelevant to the aims of this study. The other major target of sepsis research was maternal and neonatal sepsis, an area that has received more attention than

non-maternal and non-neonatal sepsis and that was included in the previous GBD Study.

The small number of community-based studies was disappointing; consequently all the studies identified and included were hospital-based. Their use raises questions about how representative the data are. For example, it is possible that such data are less likely to be representative because the rural, and usually poorer, population will be less likely to access these hospitals because of financial or transportation difficulties which results in their exclusion from the hospital population cohort [28]. As well as this limited representation it may also mean that the population denominators the studies state that have been used to calculate their estimates are also inaccurate as a hospital may overestimate how many patients have access to its services. Hospital-based studies only report results from admitted patients and consequently excludes non-admitted sepsis cases. Any amount of misdiagnosis of sepsis patients may affect the reported estimates to an uncertain degree.

Few studies exist on sepsis incidence, prevalence and mortality although several report on the etiology of sepsis; these results show detailed breakdowns of the proportion of septic infections caused by particular bacteria. The comparative abundance of such studies might be explained by their usefulness in developing specific drug vaccines, antibiotics and treatment programmes. In addition, many studies briefly describe the various sequelae associated with sepsis. **Figure 1** highlights the key aspects of the natural history of sepsis.

Integrity of the results for available epidemiological studies of sepsis

The few included studies inevitably reduce the integrity of the overall results as it becomes more challenging to determine the burden of sepsis from limited data. All efforts were made to try and obtain all the articles that were considered acceptable. Despite this, no incidence or mortality results reported from Africa and only one African study discussed the etiology of sepsis in Nigeria. Similarly, there were no studies from the Asian sub-continent or the rest of Asia, and the geographically closest incidence rates reported for the whole region were from Kuwait. The lack of results means that no clear conclusions could be drawn about sepsis across the world and only figures from isolated countries could be reported.

The few child sepsis studies probably highlight the fact that studies of neonatal sepsis were not included in this review. More reported estimates might be expected for children than adults because historically public health monitoring has been dominated by child health. With increasing child survival in developing countries and more adult deaths then the incidence of sepsis might also become a more sizeable problem. However, such a change in the burden of sepsis is expected to result in an exposure of the inadequacy of data reported for adults.

Study limitations

The current literature review was limited to studies identified in the Medline databases but could have been extended other databases, including Embase, Web of Science, Global Health Search and the French search engine LILACS, United Nations and WHO databases, non-journal based data as well as any 'gray literature' in the form of white papers, un-published research, government reports and working papers. Also, the inclusion of non-English language articles might have increased the completeness of the review. Several non-English papers were excluded and others were not considered due to a lack of an English abstract. In addition, search limitations might also have been reduced and allowed a free text search rather than a title and abstract search. This was not feasible in the present context, however, because of the sheer number of results generated.

Burden of sepsis estimates and the GBD study

The estimates highlighted in this study can have a valuable impact by themselves as well as a significant impact through the GBD study. In addition to the sepsis incidence and mortality estimates identified, additional research on prevalence and the sepsis severity could be used to then compute them into DALYs, which can help paint a picture of the gross impact of sepsis and not simply just the mortality, prevalence or the incidence in isolation. This is important as it means that sepsis will not just be viewed in terms of how many it kills but it will also include the impact that it has on patients that survive. As can be seen from the natural history diagram (**Figure 1**) there are many sequelae associated with sepsis that can have a life-long disabling impact. Having this knowledge incorporated into the DALYs will help with getting a fuller picture of the impact of sepsis in the community. Such prioritisation may manifest in several ways; it can result in a more significant presence in both regional and global policy and strategy. However, once sepsis is recognized as an important contributor to burden of mortality and ill health, funding agencies may be more likely to consider funding interventions and treatment programmes (eg, vaccine and drug development) as well as investing more in research and development associated with sepsis.

Recommendations and suggested further research

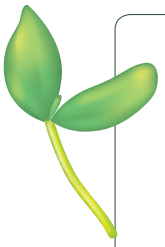
The next step is to apply the literature review strategy to other databases to ensure that the main sources of relevant data have been considered. This may also mean the inclu-

sion of foreign language articles and having particularly relevant studies translated to ensure that inclusion and exclusion criteria can be applied fully. In order to truly understand the burden of sepsis more time needs to be invested in reviewing non-journal format data including national surveillance data and other 'gray' literature available. Specifically, in light of the low results, alternative strategies should be tried as these might yield greater results. One alternative search strategy that needs considering focuses on the specific type of pathogens associated with sepsis. By conducting multiple literature reviews each focusing on a specific pathogen such as meningococcal or typhoid sepsis and gathering estimates for the incidence, prevalence and mortality of each of these forms of sepsis it may be possible then to combine them all for an overall estimate of sepsis.

CONCLUSION

Understanding the scale by which sepsis impacts the community is important. The present results show that on average sepsis is reported to have an incidence of 56-91 cases per 100 000 people, with a reported mortality rate of 30%. These estimates are accompanied by wide uncertainty bounds. This indicates that sepsis is a public health problem that the global health community needs to embrace more fully.

The limited results reported in this study highlight the need for greater investment in sepsis research and improved surveillance and reporting of sepsis cases which may also require the development of comprehensive national and international frameworks for data collection and reporting.



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Social, economic, political and health system and program determinants of child mortality reduction in China between 1990 and 2006: A systematic analysis

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Background Between 1990 and 2006, China reduced its under-five mortality rate (U5MR) from 64.6 to 20.6 per 1000 live births and achieved the fourth United Nation's Millennium Development Goal nine years ahead of target. This study explores the contribution of social, economic and political determinants, health system and policy determinants, and health programmes and interventions to this success.

Methods For each of the years between 1990 and 2006, we obtained an estimate of U5MR for 30 Chinese provinces from the annual China Health Statistics Yearbook. For each year, we also obtained data describing the status of 8 social, 10 economic, 2 political, 9 health system and policy, and six health programmes and intervention indicators for each province. These government data are not of the same quality as some other health information sources in modern China, such as articles with primary research data available in Chinese National Knowledge Infrastructure (CNKI) and Wan Fang databases, or Chinese Maternal and Child Mortality Surveillance system. Still, the comparison of relative changes in underlying indicators with the undisputed strong general trend of childhood mortality reduction over 17 years should still capture the main effects at the macro-level. We used multivariate random effect regression models to determine the effect of 35 indicators individually and 5 constructs defined by factor analysis (reflecting effects of social, economic, political, health systems and policy, and health programmes) on the reduction of U5MR in China.

Results In the univariate regression applied with a one-year time lag, social determinants of health construct showed the strongest crude association with U5MR reduction ($R^2=0.74$), followed by the constructs for health programmes and interventions ($R^2=0.65$), economic ($R^2=0.47$), political ($R^2=0.28$) and health system and policy determinants ($R^2=0.26$), respectively. Similarly, when multivariate regression was applied with a one-year time lag, the social determinants construct showed the strongest effect (beta=11.79, $P<0.0001$), followed by the construct for political factors (beta=4.24, $P<0.0001$) and health programmes and interventions (beta=–3.45, $P<0.0001$). The 5 studied constructs accounted for about 80% of variability in U5MR reduction across provinces over the 17-year period.

Conclusion Vertical intervention programs, health systems strengthening or economic growth alone may all fail to achieve the desired reduction in child mortality when improvement of the key social determinants of health is lagging behind. To accelerate progress toward MDG4, low- and middle-income countries should undertake appropriate efforts to promote maternal education, reduce fertility rates, integrate minority populations and improve access to clean water and safe sanitation. A cross-sectoral approach seems most likely to have the greatest impact on U5MR.

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Reduction of the under-five mortality rate (U5MR) has been recognized by the United Nations as one of the leading global priorities, and the fourth Millennium Development Goal (MDG4) calls on countries to reduce their U5MR by two-thirds from their 1990 baseline [1]. The latest Countdown Report finds only 19 of 68 target countries are on track to achieving this goal [2]. Evidence based guidance on the optimal mix of investments could greatly assist in accelerating progress.

Industrialized western countries achieved reductions in U5MR greater than 70% in the 30-year period between 1900 and 1930 [3-6], from baselines comparable to the rates observed in sub-Saharan African countries today [5,6]. This large decline has been attributed to economic development, improved diets and housing [7,8]. Economic progress alone, however, is not the answer; while there is clearly a correlation between U5MR and gross domestic product per capita (GDP) [9], there are many pairs of countries with 10-fold or greater difference in GDP but the same level of U5MR, and vice versa [10]. Analysis of more recent declines in child mortality have broadly identified several other key determinants of child survival, including maternal education [11-14], parental socio-economic status [15,16], public health expenditure and access to health services [14-18], sanitation and access to clean water and electricity [17], fertility rate [15,19], household income [15,19] and integration of minority population groups [14,20]. However, inconsistency and even contradiction among studies abounds and the interplay among these determinants and their relative importance in reducing U5MR remain unclear.

Most studies that have tried to identify the main drivers of U5MR reduction have relied on national-level data assembled through time series studies and indicators from nationally representative exercises such as Demographic Health Surveys (DHS) or Multi-Indicator Cluster Surveys (MICS) [11,12]. These studies were limited in their scope, the number of indicators that they used, the quality and quantity of the information available on mortality trends and the rigour of the analytic methods, thus limiting the inferences that can be drawn from them. The availability of annual child mortality data along with data related to a wide range of relevant determinants for each of 30 Chinese provinces over a 17-year period [21,22] provided the opportunity to conduct a more rigorous assessment of determinants of child mortality.

In the period between 1990 and 2006, China reduced its U5MR from 64.6 to 20.6 per 1000 live births, thus achieving MDG4 nine years ahead of schedule in a population of over 80 million under-fives [23]. This study explores the contribution of social, economic and political determinants, health system and policy determinants, and health programmes and interventions to this success using 35 indicators and provincial U5MRs from 30 Chinese provinces over the period 1990–2006.

METHODS

Data sources

For the starting year (1990), we obtained U5MR data for 30 provinces, measured as the number of under-five deaths per 1000 live births, from the Chinese national report on neonatal, infant and under-five mortality [10,22]. We believe that those baseline rates are plausible because they were derived from a nation-wide neonatal, infant and under-five mortality rate study conducted in 1990 [22]. For each year between 1992 and 2006, we obtained an estimate of U5MR for the same 30 provinces from the China Health Statistics Yearbook (CHSY) [21]. We combined Chongqing and Sichuan Province for consistency across time, because Chongqing had been under the administration of Sichuan Province and became a Municipality directly under the Central Government in 1997. The CHSY reports province level U5MR estimates based on data from China's Maternal and Child Health Annual Report system. This vital registration system collects information on births and maternal and child deaths at rural county and urban district level. A detailed description of the annual report system and its quality is available in recent publications [23-25]. The reliability of province-level U5MR estimates was much improved from 1996 onwards when the "Maternal and Infant Law" [26] was passed and the collection and management of the data were centralized by statisticians in the School of Public Health, Peking University. For further details about data sources and quality please see Online Supplementary Document (table w1). Based on an explicit set of criteria (Online Supplementary Document, table w2), we decided to impute the data in the period 1991-1995 in the 16 provinces with inconsistent data during this period. In the other 14 provinces with plausible data, the missing U5MR data for 1991 were imputed by assuming a linear trend between 1990 and 1992. Overall, 416 (81.6%) data points for the U5MR outcome variable were based on the reported estimates and 94 (18.4%) were imputed because of concerns over data quality. **Figure 1** displays the trends of U5MR in each province between 1990 and 2006.

For each study year we also obtained province-level data on different social (n = 8), economic (n = 10), political (n = 2), health system and policy (n = 9) and health programmes and intervention (n = 6) indicators, available for each province and every year. The 20 social, political and economic indicators were extracted from the National and Provincial Statistics Yearbook (NPSY) [21]. Seven of the health system indicators were identified from the CHSY

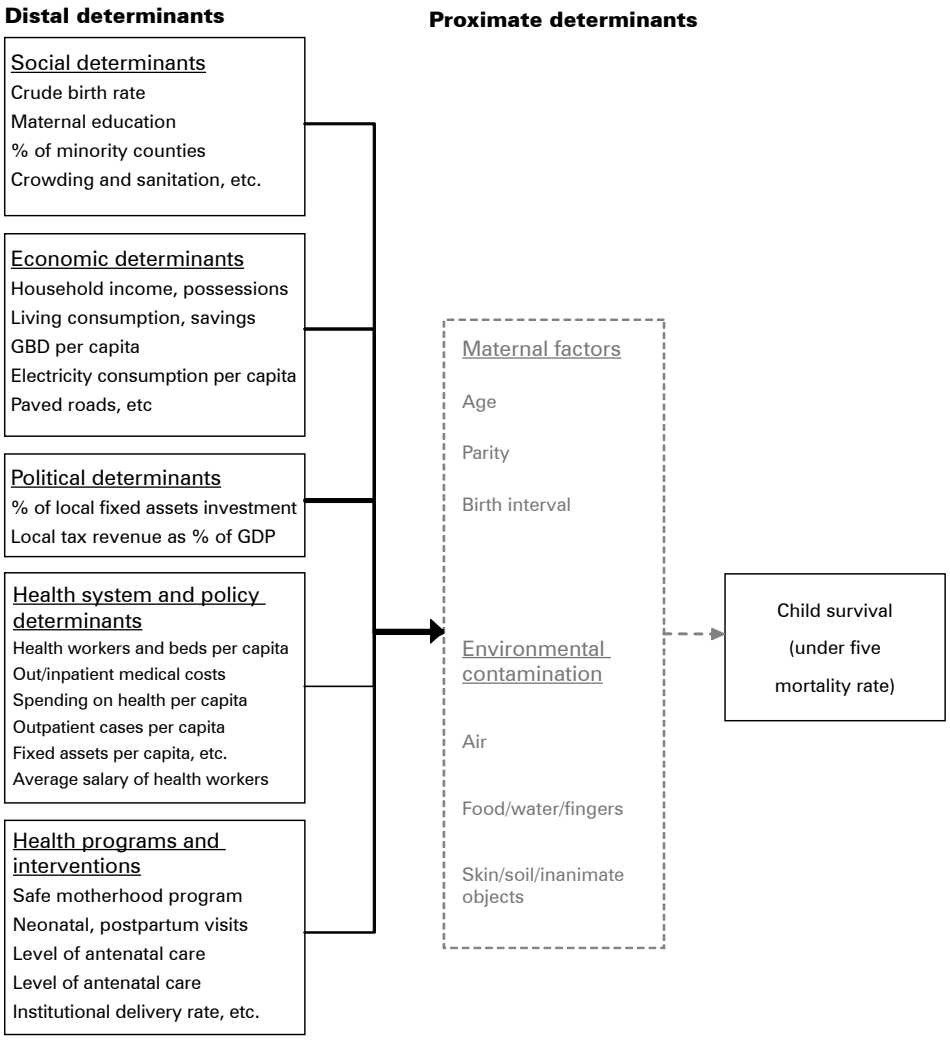

Figure 1 Conceptual framework of social, economic, political, and health system determinants of child survival. Adapted from Mosley and Chen (1984).

and the other seven were retrieved from the Health Finance Annual Report [27]. We also created a dummy variable indicating the coverage of China's Safe Motherhood Program which was initiated in 2000 in selected high U5MR provinces [24]. A detailed description of the source, definition, and measurement unit of each indicator is provided in Online Supplementary Document (tables w1 and w3).

The government data on province-level mortality and indicators are not of the same quality as some other health information sources in modern China, such as articles with primary research data available in CNKI and Wan Fang databases, or Chinese Maternal and Child Mortality Surveillance system, which were used in some of our recent high-profile publications [23-25]. Still, we believe that the comparison of relative changes in underlying indicators with the undisputed strong general trend of childhood mortality reduction over 17 years should still capture the main effects at the macro-level and should be useful for drawing very general conclusions.

Statistical analysis

A detailed description of our step-wise approach to the analysis of these data is presented in the Online Supplementary Document (table w2). We based our analysis on a conceptual framework that is adapted from the widely accepted Mosley and Chen child survival framework [28]. We conceptualized that distal determinants, including social, economic, political, health system and policy and health programs and interventions, act through a set of proximal determinants to affect child survival, as measured by U5MR. We took a reduced-form approach [29] to specifically examine the association between the 5 distal determinants and U5MR (see **Figure 2**).

Based on this conceptual framework, we first ran univariate and multivariate regression models to estimate the association between each of the 35 indicators and U5MR in each province (Online Supplementary Document, tables w4 and w5). We used a random effects linear regression model, taking into account the clustering of annual U5MR

within each province. The indicators were standardized to facilitate comparison of the regression coefficients across indicators (see Online Supplementary Document, table w2, for details).

We then grouped the 35 indicators into 5 separate categories to capture the effects of social, economic, political, health system and policy, and health programmes and interventions determinants in each province. Factor analysis was conducted to extract the main variation from variables in each group. One factor was created per group to represent the majority proportion of common variation within that group. The 35 indicators were assigned to each of the 5 factors ('constructs') based on their maximum loadings on each factor, as shown in **Table 1**.

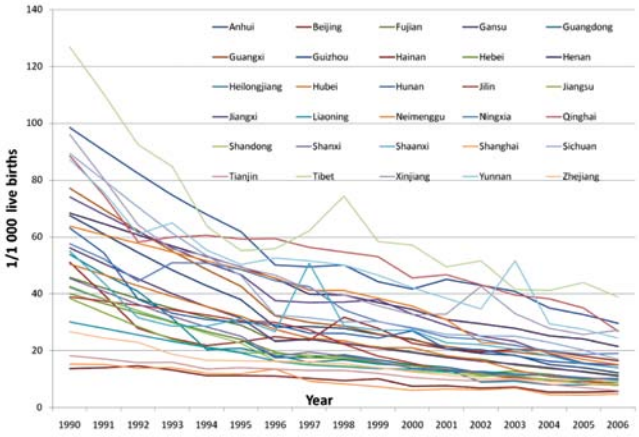

Figure 2 Trends of U5MR by provinces in China 1990-2006.

The 5 constructs, ie, the social, economic, political, health system and policy, and health programmes and interventions, were entered into the same random effects linear regression model described above. Univariate and multivariate regressions were again conducted to compare the unadjusted and adjusted associations between the 5 covariates and the province-level U5MR. To take into consideration possible time lags between changes in the 5 distal covariates and their effect on U5MR, time lags of zero and one years were applied for univariate regression, and zero, one, two and three years for multiple regression (**Table 2**).

In an attempt to gain further programmatic insights from our data, the 30 provinces were stratified into two groups using three different criteria: (i) those above and below the median rate of U5MR decline (which was -1.720 per 1000 live births per year); (ii) those above and below the median

Table 1 Loading scores of determinants in their corresponding construct

Determinants	Health construct factors				
	Health system and policy	Health program and intervention	Economic	Social	Political
Number of health workers or doctors per 1000 population	0.4456				
Number of hospital beds per 1000 population	0.3828				
Outpatient medical costs per capita	0.9657				
Inpatient medical costs per capita	0.9719				
Total spending on health per capita	0.9905				
Public spending on health per capita	0.7712				
Number of outpatient cases per 1000 population	0.4979				
Fixed assets per capita	0.9482				
Average salary of health workers	0.8493				
Institutional delivery rate		0.7490			
Level of antenatal care		0.7953			
Level of postpartum visit		0.9010			
Level of neonatal visit by physician		0.7762			
Child care systematic management rate		0.7751			
Safe Motherhood Program indicator		0.0308			
Urban household income			0.9346		
Rural household income			0.9716		
Urban living consumption			0.9095		
Rural living consumption			0.9549		
Household possessions index			0.9277		
Bank savings per capita			0.9288		
GDP per capita			0.9710		
Electricity consumption per capita			0.7998		
Paved roads per square kilometres			0.7686		
Cargo turnover per capita			0.5743		
Percentage of autonomous ethnic minority counties				0.5605	
Illiteracy rate of women aged 15+				0.7103	
Crude birth rate				0.8481	
Urban household crowding				0.4663	
Rural household crowding				0.7781	
Percentage of household with clean water				–0.6631	
Hygienic toilet coverage				–0.7656	
Population density				–0.5710	
Proportion of local fixed assets investment					–0.7071
Local tax revenue as % of GDP					0.7071
Proportion of common variation accounted	0.7590	0.9000	0.9066	0.8414	0.6804

Table 2 Unadjusted and adjusted association between U5MR and the social, economic, political and health system determinants, by time lag

Determinants	Univariate regression		Multivariate regression			
	No lag	1 year lag	No lag	1 year lag	2 year lag	3 year lag
Health system and policy factor						
Beta (95% CI)	−9.426 (−10.946, −7.905)‡	−9.415‡ (−10.952, −7.879)	3.555‡ (1.052, 6.059)	4.109‡ (1.448, 6.771)	4.511‡ (1.746, 7.276)	5.450‡ (2.565, 8.336)
Constant (95% CI)	30.061 (25.704, 34.419)‡	27.683‡ (23.533, 31.834)				
R^2	0.252	0.256				
Health programmes and interventions factor						
Beta (95% CI)	−16.559 (−17.697, −15.421)‡	−13.936‡ (−14.994, −12.879)	−5.044‡ (−6.486, −3.602)	−3.452‡ (−4.778, −2.126)	−2.302‡ (−3.529, -1.075)	−1.228† (−2.377, −0.079)
Constant (95% CI)	30.061 (27.289, 32.834)‡	27.894‡ (25.273, 30.516)				
R^2	0.660	0.649				
Economic factor						
Beta (95% CI)	−11.984‡ (−13.146, −10.822)	−11.773‡ (−12.908, −10.638)	−1.827 (−4.875, 1.221)	−2.084 (−5.357, 1.190)	−2.358 (−5.732, 1.017)	−3.059* (−6.494, 0.375)
Constant (95% CI)	30.061‡ (26.437, 33.686)	27.302‡ (23.803, 30.801)				
R^2	0.466	0.468				
Social factor						
Beta (95% CI)	18.307‡ (17.247, 19.368)	16.304‡ (15.349, 17.259)	11.676‡ (9.642, 13.709)	11.787‡ (9.868, 13.705)	11.418‡ (9.626, 13.210)	11.470‡ (9.742, 13.199)
Constant (95% CI)	30.061‡ (27.600, 32.523)	27.534‡ (25.222, 29.846)				
R^2	0.728	0.740				
Political factor						
Beta (95% CI)	17.566‡ (16.080, 19.051)	14.189‡ (12.843, 15.535)	6.013‡ (4.587, 7.440)	4.241‡ (2.930, 5.552)	3.071‡ (1.861, 4.280)	2.225‡ (1.090, 3.360)
Constant (95% CI)	30.061‡ (25.230, 34.893)	28.049‡ (23.488, 32.611)				
R^2	0.315	0.276				
Constant						
			30.061‡ (27.820, 32.303)	27.663‡ (25.530, 29.795)	25.546‡ (23.512, 27.581)	23.708‡ (21.745, 25.671)
R^2			0.786	0.782	0.778	0.777
No. of observations	510	480	510	480	450	420

U5MR – under-five mortality rate, CI – confidence interval

*$P<0.10$.

†$P<0.05$.

‡$P<0.01$.

U5MR in 1990 (which was 54.5 per 1000 live births); and (iii) those above and below the median GDP per capita in 2006 (which was US$ 1709). We conducted multivariate analyses (stratified analyses with 1-year time lag) of the 5 constructs separately in each subset of 15 provinces to identify the key determinants of child mortality reduction in different contexts (**Table 3**).

RESULTS

Between 1990 and 2006, the U5MR decreased substantially in all 30 provinces in China (**Figure 1**). It varied more than 9-fold across provinces in 1990, ranging from 13.7 to 126.7 per 1000 live births. In 2006 the variability in U5MR was still more than 8-fold, ranging from 4.81 to 38.9 per 1000 live births.

Among the crude and adjusted associations between the 35 indicators and U5MR based on 510 data points (ie, 30 provinces × 17 years) the strongest crude associations were observed for the indicator 'hospital delivery rate" ($R^2=0.72$), 'crude birth rate" ($R^2=0.67$), 'child care systematic management rate" ($R^2=0.62$), 'household possession index" ($R^2=0.57$) and 'illiteracy rate of women aged 15+' ($R^2=0.56$) (Online Supplementary Document, table w4). In multivariate regression with all 35 determinants included, 88% of the overall variance in U5MR was explained by all 35 indicators (Online Supplementary Document, table w5).

Factor analysis showed that within each of the social, economic, political, health system and policy, and health programs and interventions constructs, all the indicators correlated well with the resulting factor (as suggested by the large factor loadings). Each of the 5 extracted factors captured 68–91% of the common within-group variation of its affiliated indicators (**Table 1**).

Crude and adjusted associations between U5MR and these 5 constructs are presented in **Table 2**. In the univariate analysis with one-year time lag, determinants within the social construct showed the strongest crude association with U5MR reduction ($R^2=0.74$), followed by strong effects of health programmes and intervention ($R^2=0.65$), economic determinants related to both population and local governments ($R^2=0.47$), political determinants as measured by decentralization indices ($R^2=0.28$) and health system and policy determinants ($R^2=0.26$). When multivariate regres-

sion was applied with a one year time lag, 78% of the variation in the system was explained by the 5 constructs. Again, the social determinants showed the strongest effect (beta = 11.79, $P<0.0001$), followed by political determinants (beta = 4.24, $P<0.0001$), and health programmes and interventions determinants (beta = –3.45, $P<0.001$). Health system and policy determinants had a counter-intuitive adjusted effect (beta = 4.11, $P<0.0025$) and the effect of economic factor was not statistically significantly different from 0 (beta = –2.08, $P=0.2123$) (**Table 2**).

The associations showed distinctive patterns of change when different time lags (0-3 years) were applied (**Table 2**). Social determinants were the only construct that did not seem sensitive to the time lag applied. The effects of health programmes and intervention determinants and political determinants diminished as the time lag increased from 0 to 3 years (beta values: –5.0, –3.4, –2.3, –1.2, and 6.0, 4.2, 3.1, 2.2, respectively). At the same time, the importance of health system and policy determinants and economic determinants increased steadily (beta values: 3.5, 4.1, 4.5, 5.5, and –1.8, –2.1, –2.4, –3.1, respectively). Our interpretation of this finding, which is important for health planning and resource allocation, is that social determinants of child survival act both within a short and mid-term period. The effects of health programmes, interventions and political budgetary decisions are more likely to be felt within a short time period. The effects of economic growth and investments into health systems also contribute substantially to child mortality reduction, but they require a mid-term period to be detected in full.

Table 3 reports the results of the analyses stratified by U5MR decline, U5MR and GDP (as described above) with a 1 year time lag (the results for other studied time lags are shown in the Online Supplementary Document, table w6). The notable change was the increased importance of determinants in the health systems and policies construct in the sub-group of provinces that started with lower U5MR, higher GDP and slower declines in U5MR. With a few exceptions, the determinants in the social construct were nearly always associated with the largest contribution to U5MR reduction (beta range 5.6 to 11.9). Economic factors have a positive role in the reduction of child mortality across all 6 strata (beta range –3.9 to –12.6), followed by health programs and intervention determinants (beta range 0.1 to –4.1). However, the associations of determinants in the health program and intervention construct with U5MR differed across stratified groups. They seemed to have most importance in the 15 provinces with higher starting U5MR and lower GDP. The effect of political determinants was significant in the provinces with higher starting U5MR and faster rate of U5MR decline. In the 15 provinces with a faster-than-median rate of U5MR decline, economic determinants were the strongest factors independently associated with U5MR (one-year lag model beta = –12.5, $P<0.001$), followed by social determinants (beta = 6.1, $P<0.001$). The same pattern was observed in the study of association between the 5 constructs and U5MR in the 15 provinces with above-median baseline U5MR level (economic determinants: beta = –12.6, $P<0.001$; social determinants: beta = 5.6; $P<0.001$), and with below median levels of GDP

Table 3 Adjusted associations between U5MR and the social, economic, political, health system determinants with 1 year lag after stratifying by U5MR rate of decline, level of U5MR in 1990 and GDP per capita level in 2006

Determinants	U5MR rate of decline		U5MR in 1990		GDP per capita in2006	
	≤median†	>median	≤median†	>median	≤median‡	>median
Health system and policy factor						
Beta (95% CI)	6.784 (4.737, 8.831)‡	1.002 (–4.573, 6.578)	7.623‡ (5.521, 9.724)	–0.098 (–5.421, 5.226)	–1.954 (–8.415, 4.507)	5.499‡ (3.188, 7.809)
Health programmes and interventions factor						
Beta 95% (CI)	–2.852‡ (–4.107, –1.596)	–2.964‡ (–4.828, –1.101)	0.047 (–1.204, 1.298)	–3.820‡ (–5.668, –1.972)	–4.121‡ (–6.059, –2.184)	–1.06 (–2.529, 0.409)
Economic factor						
Beta (95% CI)	–6.640‡ (–9.373, –3.907)	–12.535‡ (–18.651, –6.418)	–8.293‡ (–11.145, –5.440)	–12.581‡ (–18.241, –6.920)	–9.400‡ (–15.657, –3.143)	–3.865† (–6.960, –0.770)
Social factor						
Beta (95% CI)	7.869‡ (6.046, 9.693)	6.120‡ (2.930, 9.310)	8.384‡ (6.706, 10.063)	5.610‡ (2.470, 8.750)	5.628‡ (2.359, 8.896)	11.901‡ (9.830, 13.972)
Political factor						
Beta (95% CI)	0.863 (–0.293, 2.020)	4.821‡ (2.837, 6.804)	0.955 (–0.463, 2.373)	3.639‡ (1.896, 5.382)	4.218‡ (2.220, 6.217)	2.307‡ (0.901, 3.713)
Constant						
Beta (95% CI)	23.108‡ (20.870, 25.347)	28.115‡ (24.797, 31.434)	21.731‡ (20.492, 22.969)	28.139‡ (24.889, 31.390)	27.166‡ (23.575, 30.757)	23.841‡ (21.480, 26.201)
R^2	0.774	0.792	0.761	0.792	0.750	0.820
No. of observations	240	240	240	240	240	240

U5MR – under-five mortality rate, GDP – gross domestic product, CI – 95% confidence interval

*$P<0.10$.

†$P<0.05$.

‡$P<0.01$.

§The median of the rate of decline was –1.720 per 1000 live births per year.

¶The median of U5MR in 1990 was 54.5 per 1000 live births.

||The median of GDP per capita in 2006 was US$ 1708.8 (2006 value).

per capita (economic determinants: beta = –12.6, $P<0.001$; social determinants: beta = 5.6; $P<0.001$) (**Table 3**).

We conducted several additional sensitivity analyses to examine the robustness of our reported results. We reclassified the 'crude birth rate' indicator from the social to health system and policy construct (Online Supplementary Document, table w7). Although this indicator increased the overall effect of the latter construct substantially across all 4 time lags, the construct with social indicators remained the most significant determinant of child survival reduction. This analysis gave 2 important results: (i) the large effect of social determinants on child survival reduction is not dependent on fertility reduction; and (ii) fertility reduction has a very strong independent effect on child mortality. We also repeated the multivariate analysis after excluding the indicators that were not associated with U5MR in the univariate analysis (Online Supplementary Document, table w8), again with little overall change to the main conclusions. Finally, we ran the analysis only using data for 1996–2006, to avoid any biases that may have been introduced by use of imputed trends in 16 provinces in the 1991–1995 period (Online Supplementary Document, table w9). None of these analyses generated substantially different results. We presented the immunization coverage for all main vaccines against childhood diseases in the 1990–2006 period, to demonstrate that vaccination rates remained consistently very high with little variation throughout the study period and were thus not expected to influence our results (Online Supplementary Document, table w10).

DISCUSSION

We are not aware of any other studies of this scale that have explored the impact of many diverse determinants of child survival in large child populations over an extended period of time, during which genuine progress in U5MR reduction has been achieved. The results of our analysis showed that the identified determinants accounted for almost 90% of the observed U5MR reduction during the years examined.

Importance of social determinants

The fall in U5MR observed in China since 1990 was most influenced by social determinants – although the health system, health program, political and economic determinants also had important and independent roles. Along with the creation of the community-based "barefoot doctor" health providers in rural areas (whose role also included also promotion of literacy, sanitation and hygiene), which was hailed as one of the foundations of the primary health care movement [30,31], the Chinese government launched effective efforts to control population growth even before the one-child policy. Those efforts had already halved the total fertility rate from 5.9 to 2.9 by 1979 [32,33]. Although good quality child mortality data are not available for China from 1950–1980, available data report a large reduction in infant mortality rate from about 250 per 1000 live births in 1950 to 50 by 1980 [34]. Based on our analysis, the continuing decline in China's U5MR owes much to its broad social progress and political stability, with economic development also benefiting from these determinants, and in turn influencing the number of child deaths prevented [21,22,27,34].

Importance of fertility decline

Our results suggest that China's success in reducing fertility rates and the resulting community approaches to improved parenting and protection of child health had a major influence on child mortality. Although it is difficult to isolate this factor and make secure inferences about its independent effects, we found that fertility rate had the highest loading on the "social factor" cluster, which itself explained most of child mortality reduction. In these circumstances the effects of the other determinants that we studied may be attenuated in other countries in the absence of the level of fertility rate reduction observed in China. This hypothesis is reinforced by the sensitivity analysis presented in the Online Supplementary Document, table w7, where the indicator of fertility decline was moved to the health systems and policy construct where it substantially increased the effect size of this construct. There have been debates about the direction of the causal association between fertility reduction and child mortality reduction [35,36]. We believe that the example of China, where fertility was dramatically and suddenly reduced by law regardless of the second variable (U5MR), which then led to large reduction of U5MR during the following two decades, represents strong evidence in favor of a causal role of effective fertility measures on child mortality reduction.

Variability of the impact of determinants of child mortality reduction

Social determinants seemed to be strongly associated with the reduction in U5MR when all 30 provinces, 35 indicators and 17 years were included in the analysis, closely followed by determinants in the health programmes and interventions construct. However, more detailed analyses revealed several interesting findings relevant for health policy and planning. If short-term effects are required, investments are better placed in social determinants, health programmes and interventions, and political determinants that include empowerment of local governments. However, if more strategic and long-term effects are expected, investments should once again support social determinants, but also health system development and economic development. In the context of a high baseline U5MR, low GDP and a planned rapid rate of U5MR decline, the greatest ef-

fect should be expected from action on economic and social determinants, but also health programmes and interventions and political determinants. However, in the context of low U5MR, higher GDP and a planned moderate rate of U5MR decline, the greatest effect should be expected from action on social determinants and health system and policy determinants. These findings are consistent with previous observations on similar data sets [15,18].

Limitations of the study

There were many interesting potential determinants which we could not study in the absence of reliable year-to-year information. This includes immunization rates, although we performed a separate analysis of their likely effects on our overall results (Online Supplementary Document, table w10). We would have also liked to investigate the effects of more specific health-program variables (for example child nutrition status and practices, management of diarrhea and pneumonia, vitamin A supplementation), more detailed data on maternal education level, levels of health facility access and use, health insurance coverage, poverty thresholds, corruption indices, and many others [37-40]. None of these were included because we could not, at the time of analysis, obtain reliable information on any of these indicators from Chinese information sources. In this study, we used only indicators for which the available data during the period 1990–2006 suggested a level of completeness and reliability that would allow sufficient statistical power to address the main aims of this study. The Online Supplementary Document shows the approaches and sensitivity analyses that we used to assure and verify the quality of our input data.

This Chinese example, in which child health inequities do not appear to have been widening over the past 15 years, is important as a case study in the wider global context [41,42]. We suggest there would be value in encouraging other nations to collate a similar set of determinants (for example through large scale intermittent surveys such as serial MICS and DHS augmented with data from other sources) and then apply the conceptual framework and methodology we adopt in this study. There have already been a few good reports of such analyses in the literature [15,43-45].

While we employed many excellent indicators to capture social, economic, health systems and policy, and health programmes and interventions determinants of U5MR reduction, it is very difficult to evaluate the impact of political determinants in the same way. We believe that our two political indicators represented a proxy of the level of decentralization and the spending power of the local governments. However, we believe that the mismatch between local resources and spending responsibilities in the absence of adequate central-local grants / transfers at the provincial and sub-provincial levels is an important political issue which may, in large part, explain why insufficient public resources are employed to target social and health indicators in poor localities [46]. Given the wide disparities within provinces, the provincial GDP per capita may have little impact on the living conditions (and U5MR) in remote 'pockets of poverty' within provinces. Future analyses should seek to extend and develop more appropriate indicators of political determinants to better reflect the well documented imbalance between available resources and spending responsibilities at the provincial and sub-provincial levels in China. Given the size of China's provinces, such analyses will be highly relevant to similar analyses at country level elsewhere, and should contribute to reforms in the equity of public resource allocation.

CONCLUSION

The results presented in this study support the recent calls to broaden vertical programs to include strengthening of health systems [47,48]. However our research suggests that this approach also has its limitations, as it potentially ignores the broader social, economic and political determinants that impact on all sectors of society. In addition to maternal and child health and nutrition programs, approaches to reducing child mortality should also incorporate improvements in general literacy and particularly education of women; access to fertility control options; access to clean water and sanitation; integration of minority populations, along with ensuring underlying political stability and good governance. As many of these determinants are not traditionally under the purview of health authorities, there is a risk that those determinants are inadequately considered in national approaches to reducing child mortality. An analysis of the relative importance of these and other determinants, if data are available, and the further study of the possible reasons for their impact, may help explain large disparities between the U5MRs of nations with similar rates of economic development. It may also explain the difficulty in further reducing U5MR after communicable disease mortality is controlled by disease-specific and other health- and nutrition-focused interventions. The WHO Commission on Social Determinants of Health was a step toward an analysis of these factors [49,50], but without convincing attempts until now to apply this approach to a key child health indicator such as U5MR.

In conclusion, this analysis has shown that China has achieved its remarkable progress in reducing U5MR through an inter-sectoral approach made possible through political stability over a prolonged period of time. The key characteristics of child mortality reduction were sustained economic growth and a focus on social development alongside key investments in health systems and expanded health intervention coverage.

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Authorship declaration: IR, XLF, KYC, LL, YG and HC designed the study. XLF, LL and ET conducted the analyses. IR, KYC, YG, HC, XLF, ET and LL drafted the paper with other various authors' contribution in revision. XLF and YG conducted the systematic review of the available evidence in Chinese language and data extraction from Chinese databases. RS, DH, HB, WC, SG, MC and REB provided important intellectual and material input at different stages of the work and contributed to drafting the paper.

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Understanding the determinants of the complex interplay between cost-effectiveness and equitable impact in maternal and child mortality reduction

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Background One of the most unexpected outcomes arising from the efforts towards maternal and child mortality reduction is that all too often the objective success has been coupled with increased inequity in the population. The aim of this study is to analyze the determinants of the complex interplay between cost-effectiveness and equity and suggest strategies that will promote an impact on mortality that reduce population child health inequities.

Methods We developed a conceptual framework that exposes the nature of the links between the five key determinants that need to be taken into account when planning equitable impact. These determinants are: (i) efficiency of intervention scale-up (requires knowledge of differential increase in cost of intervention scale-up by equity strata in the population); (ii) effectiveness of intervention (requires understanding of differential effectiveness of interventions by equity strata in the population); (iii) the impact on mortality (requires knowledge of differential mortality levels by equity strata, and understanding the differences in cause composition of overall mortality in different equity strata); (iv) cost-effectiveness (compares the initial cost and the resulting impact on mortality); (v) equity structure of the population. The framework is presented visually as a four-quadrant graph.

Results We use the proposed framework to demonstrate why the relationship between cost-effectiveness and equitable impact of an intervention cannot be intuitively predicted or easily planned. The relationships between the five determinants are complex, often non-linear, context-specific and intervention-specific. We demonstrate that there will be instances when an equity-promoting approach, ie, trying to reach for the poorest and excluded in the population with health interventions, will also be the most cost-effective approach. However, there will be cases in which this will be entirely unfeasible, and where equity-neutral or even inequity-promoting approaches may be substantially more cost-effective. In those cases, investments into health system development among the poorest that would increase the quality and reduce the cost of intervention delivery would be required before intervention scale-up is planned.

Conclusions The relationships between the most important determinants of cost-effectiveness and equitable impact of health interventions used to reduce maternal and child mortality are highly complex, and the effect on equity cannot be predicted intuitively, or by using simple linear models.

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In recent years, enormous efforts have been made to estimate the global burden of maternal and child mortality and identify the main causes, study the role of risk factors, assess the effectiveness of available interventions, and to track the coverage of those interventions in low and middle-income countries [1-10]. However, this large body of evidence has not been followed by the development of sufficiently simple and accurate tools and approaches that effectively translate the evidence and information into health policy decisions where this is most needed – at the national and sub-national level in low-resource settings. In the absence of evidence-based planning, it is not surprising that unexpected outcomes can arise from efforts towards maternal and child mortality reduction. One of the most perplexing outcomes is that all too often the objective success in mortality reduction has been coupled with an increased health inequity in the population [11].

To understand the roots of this problem, we should appreciate that policy makers at the national and sub-national level have limited resources for scaling up cost-effective health interventions in their populations. When planning the "best buys" for committing their resources in maternal and child health, they are faced with a very complex task. They need to choose between at least several dozen interventions that target neonates, infants, children and mothers, most of which have been proven to be cost-effective in many contexts [4,5,8,9]. They soon realize that it would take more than a simple calculation to decide on the most rational way to invest in health intervention scale up. Depending on the local and national context, the interplay between many important factors will affect both cost-effectiveness and the impact on equity for their chosen intervention scale-up programs. Neglect (or improper understanding) of these complexities can lead to decisions which result in maternal and child mortality reduction not being achieved in the most cost-effective way, or being associated with increases in health inequity within communities. The present set of tools does not sufficiently capture the full array of factors [12].

The aim of this study is to analyze the determinants of the complex interplay between cost-effectiveness and equity in maternal and child mortality reduction and suggest strategies that promote an impact on mortality that will reduce population child health inequities. To achieve this aim, we develop a transparent framework based on several key epidemiological concepts that can be used to support national-level decision making in health intervention prioritization. Using this framework, we try to expose the complex interplay among factors that influence both cost-effectiveness and equity in child and maternal mortality reduction and identify the key information needs for planning of equitable and cost-effective programs of health intervention scale-up.

METHODS

The cost of intervention scale-up in different equity strata

The first important determinant to consider is *the cost of intervention scale-up in different equity strata*. In our framework, we will divide any population of interest into 5 equity strata (quintiles), each comprising 20% of the population, where Q1 denotes the wealthiest quintile and Q5 the poorest. The cost of achieving complete coverage with any health intervention will clearly differ between the wealthiest (Q1) and the poorest (Q5) quintile, but there is remarkably little information available on the determinants of these costs in each quintile and the actual differences in cost of implementation. It is also clear that these differences between strata will be intervention-specific and also context-specific, rather than following any "standard", predictable pattern. This means that, for some interventions, the costs may not increase dramatically (from the wealthiest to the poorest quintile) with increasing coverage. In fact, wherever the salary of health professionals is the main component of the cost, then it is possible to envisage circumstances in which, for some interventions, it may be even cheaper to cover the poorest quintile (eg, when there is a well-developed network of village health workers who can administer cheap antibiotic treatment) than the wealthiest quintile (where this depends on skilled medical doctors who have access to both cheap and more expensive antibiotics). However, there will also be many examples where complete intervention coverage will be more readily achieved among the wealthy Q1 than in the poorest Q5, where it may be almost impossible or even unfeasible to achieve.

Figure 1 summarizes this relationship. The horizontal axis represents the increasing cost required for scaling up of an intervention, while the vertical axis measures the completeness of coverage in each equity quintile (ranging from 0% to 20% of the total population). Recently, substantial efforts have been made to track the coverage of interventions specifically by equity strata in many low and middle-income countries. This work has indicated that this is an important component that will be need to be included in planning the equitable delivery of interventions [13-15]. However, we still need information on the actual cost components of intervention scale-up and how these differ across wealth quintiles in varying contexts and for each intervention. In reality, this cost cannot be expressed as a fixed amount in US$ per person that is characteristic of each delivered intervention, nor does it increase linearly as the achieved population coverage increases (**Figure 1**). The cost of intervention scale-up includes more than just the market cost of an intervention (such as vaccine or a drug), because the successful delivery also requires everything else that is re-

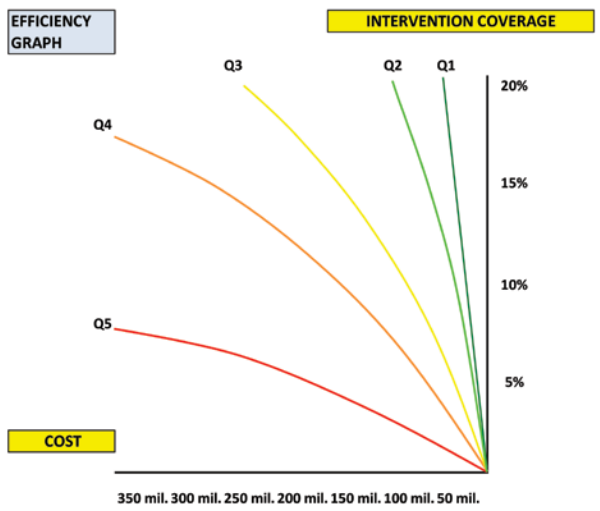


Figure 1 The relationship between cost of the intervention scale-up and achieved intervention coverage, which determines the efficiency of intervention delivery, presented for each of the five equity strata in the population (Q1 – the wealthiest quintile; Q5 – the poorest quintile).

quired to reach the targeted recipients, such as costs of health worker salaries, transport and storage, improved access and expanded outreach.

Those additional costs may be relatively small if the aim was to cover the most accessible 20% or 40% of mothers and children. In these circumstances the relationship between cost and achieved coverage may indeed be approximately linear. However, additional costs of intervention delivery will start increasing in complex and nonlinear patterns when the coverage of the most deprived children and mothers is attempted, because many obstacles need to be overcome to reach them. Because of these additional costs, all too often we observe that the most accessible mothers and children are being covered with ever more interventions, while the marginalized are missing out on all of them. This approach would still be expected to reduce maternal and child mortality, but the progress would be very slow and inequitable. This is because most child and maternal deaths occur among the most inaccessible parts of the population and only a minor part of the mortality burden is being targeted with interventions. The progress that is being achieved benefits only those who are accessible, thus increasing inequity. Reducing the additional costs of intervention delivery when targeting the poor would involve challenges that are related to both supply and demand for the prioritized interventions.

One examples of this relationship between cost and achieved intervention scale-up by equity quintiles (Q1-Q5) is shown in **Figure 1.** This graph summarizes the *efficiency* of intervention delivery. In this hypothetical example, it is apparent that for the same intervention it is much cheaper, and therefore more efficient, to achieve full coverage in the most wealthy 20% of the population (Q1) than in the poorest quintile (Q5). In fact, in this example the difference in cost is so large that it poses a question whether the potential for mortality reduction in the poorest quintile (Q5) justifies such an inefficient delivery of a life-saving intervention at such a high cost? Sometimes, even when the equity argument is being respected, it may still be entirely unfeasible to attempt to reach the poorest Q5, because the infrastructure that would allow this in a cost-effective way simply does not exist. In such cases, investing in health system development may need to precede investing in intervention coverage. We will move through the rest of the framework to explore this further, because the answers will rarely be intuitive.

The effectiveness of an intervention in different equity strata

The second determinant of cost-effectiveness and equity to consider is *the effectiveness of an intervention in different equity strata.* The effectiveness of an intervention, or its "potential impact fraction", indicates which proportion of the current mortality burden that is targeted by an intervention would be averted among those who receive the intervention, in comparison to those that do not receive it. In theory, the effectiveness of an intervention in relation to a specific cause of death – such as a specific antibiotic treatment against childhood pneumonia – should be relatively similar in all settings. This is because it should primarily be determined by the biology of disease and the interplay between the disease and the intervention. However, the experience from the field tells us that the effectiveness of the same intervention may differ substantially between Q1 and Q5. Some of the reasons may be, in the above example, that there is different spectrum of pathogens among the very poor (and less well nourished) (Q5), and /or higher levels of antibiotic resistance, and/ or later presentation with more severe symptoms because of barriers in access to care or differences in care-seeking behaviour, all of which reduces the effectiveness of antibiotic treatment against pneumonia in comparison to Q1 children. In addition, and perhaps even more importantly, the quality of intervention delivery will not be the same in all socio-economic strata. Incomplete or inadequate delivery will be more likely among the poorest (Q5), which will decrease the effectiveness of the intervention against the same cause of death. Taking the example of pneumococcal and Hib vaccine against pneumonia, this may be because of more likely interruption of the cold chain when trying to reach the poorest, lower level of health workers' education and skills which may lead more often to inadequate administration of vaccines, and lower health awareness among the parents of the children leading to lower levels of full attendance for all immunization appointments.

We tried to capture this complex relationship between the achieved coverage by equity quintiles and the effectiveness in mortality reduction in **Figure 2**. In order to expose the continuum of relationships and effects that the important determinants in this framework have on mortality reduction and equity, the vertical axis is taken from **Figure 1**. It again shows the achieved coverage by each equity quintile, which can range from 0 to 20%. The horizontal axis shows the effectiveness of the intervention of interest in terms of reduction in mortality in each equity stratum (expressed as a proportion of the total mortality in that stratum) that could be achieved for a given level of coverage shown on the vertical axis. The value on the horizontal axis where the coverage in Q1 becomes complete (in this case, between 50% and 60%) shows the maximum potential for the intervention to reduce mortality against a specific cause under ideal conditions. For example, if the cause of death of interest is pneumonia; if 50%-60% of pneumonia deaths in this setting are caused by *Pneumococcus*; and if pneumococcal vaccine is nearly 100% effective in preventing pneumococcal pneumonia deaths, then this is the maximum potential effectiveness of pneumococcal vaccine under ideal conditions. However, the adverse factors explained above (interruption of the cold chain, inadequate administration by health workers, failure to comply with full vaccination schedule by the parents) may act to reduce its effectiveness to only 20%-30% among the poorest section of the population in Q5, even when the full coverage is achieved (**Figure 2**). Presently, there is remarkably little understanding or evidence about the nature and scale of differences in effectiveness of health interventions in different equity strata, although this is one of the most important determinants of overall cost-effectiveness and equitable impact.

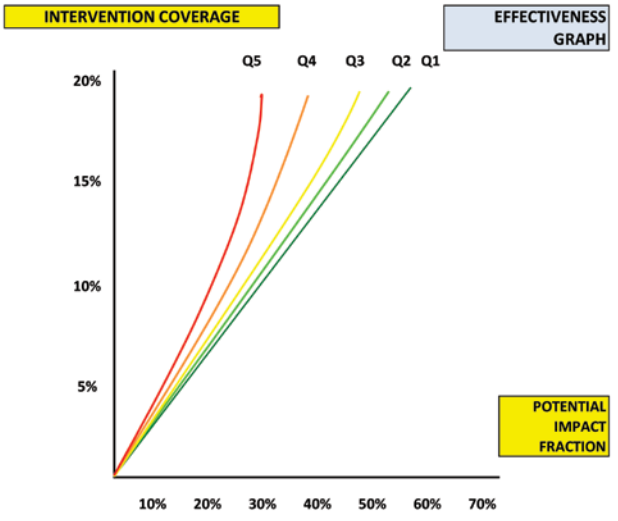


Figure 2 The relationship between achieved intervention coverage and potential impact fraction, which determines the effectiveness of the intervention, presented for each of the five equity strata in the population (Q1 – the wealthiest quintile; Q5 – the poorest quintile; to expose the continuum of relationships and effects that the important determinants in this framework have on mortality reduction and equity, the vertical axis is taken from **Figure 1**, while the horizontal axis measures the effectiveness in different equity strata).

The size and composition of the mortality burden in different equity strata

The third important determinant to consider is the *absolute size of the mortality burden in different equity strata and its composition*. The relationship between the burden of mortality and equity strata is rather predictable: the absolute number of deaths will always be much greater in the poorest (Q5) than in the wealthiest quintile (Q1), given that the quintiles are of the same size by definition (ie, 20% of population), and that mortality rates are greater among the poor. However, the graph that captures this relationship (**Figure 3**) may still look very differently, depending of the level of inequity in the population. The lines representing the five equity strata in this graph may be relatively close to each other such as in a situation where the burden of mortality is, in absolute terms, only 2 times greater in Q5 compared to Q1. However, these lines could also be far apart such as when the burden of mortality is 10 times greater in Q5 than in Q1. In a sense, **Figure 3** is a visualization of the level of inequity in a society when expressed as bearing the burden of mortality. A substantial effort has been invested in recent years to understand and explore the differences in mortality rates between the equity strata in low and middle-income countries [9,14,16,17].

There is another factor that adds complexity to the relationship between intervention effectiveness and number of deaths averted by equity strata, as shown in **Figure 3**. The breakdown of the overall number of deaths by cause of death may differ quite substantially between equity quintiles. For example, causes of deaths among the wealthiest children will be dominated by congenital abnormalities, preterm birth complications and accidents – ie, the problems that even well-functioning health system still can't easily tackle effectively. However, the poorest children will mainly be expected to die from infectious causes, such as pneumonia, diarrhea, malaria and neonatal sepsis. As an example, the proportional contribution of pneumonia to all child deaths observed in a developing country would typically be around 10% in the wealthiest quintile of children rising to up to 40% among the poorest children [18]. This is why the "potential impact fraction" of an intervention that only targets pneumonia in reduction of the overall child mortality burden could be much larger in the poorest (Q5) than in the wealthiest quintile (Q1) despite lower quality of delivery in Q5 settings acting to reduce the intervention effectiveness.

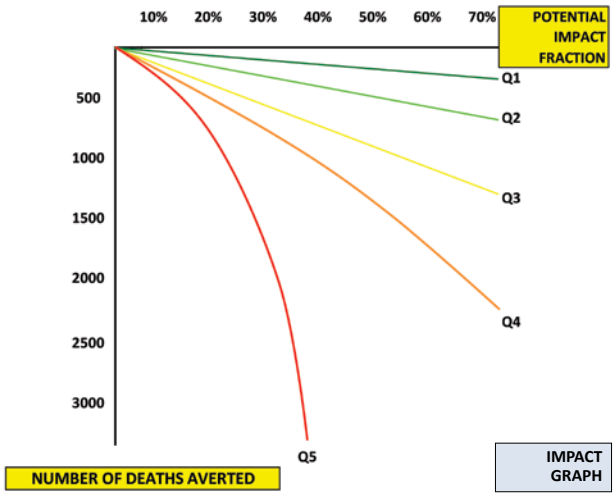


Figure 3 The relationship between potential impact fraction and number of deaths averted, which determines the potential impact of the intervention in mortality reduction, presented for each of the five equity strata in the population (Q1 – the wealthiest quintile; Q5 – the poorest quintile; to expose the continuum of relationships and effects that the important determinants in this framework have on mortality reduction and equity, the horizontal axis is taken from **Figure 2**, while the vertical axis measures the number of deaths that could potentially be averted in different equity strata).

The graph presented in **Figure 3** therefore exposes the *potential impact* of intervention delivery to reduce the burden of mortality in absolute terms. In the hypothetical case shown in **Figure 3**, it is apparent that for an intervention that targets eg, infectious causes, it is usually more effective to achieve full coverage in the poorest 20% of the population, regardless of the reduced effectiveness because of poorer quality of delivery. However, for interventions that target causes of deaths that are more prominent among the wealthiest, such as eg, congenital abnormalities, these relationships would be inverse. Similarly, if a cause of death is equally important in all 5 strata, then the effectiveness of an intervention would usually be greater among the wealthy, because the lower quality of delivery and increased barriers to access and care-seeking would reduce it among the poor.

The cost-effectiveness of investing in different equity strata

The fourth determinant to consider is the one that usually drives policy decisions: *the number of deaths averted per cost of intervention scale-up in different equity strata*. Health investors usually like to know how many deaths could be averted with a fixed level of investment. The more deaths averted per fixed investment, the more cost-effective the scale up. Therefore, **Figure 4** exposes the *cost-effectiveness* of many competing investment options.

Figure 4 is drawn using the "cost" from **Figure 1** as a horizontal axis, and "the number of deaths averted" from **Figure 3** as the vertical axis. When the cost is low and the number of averted deaths high (ie, the bottom-right corner of **Figure 4**), the intervention scale-up is highly cost-effective. When the cost is high and the number of averted deaths low (ie, the top-left corner of **Figure 4**), the intervention scale-up is not cost-effective. In **Figure 4**, the hypothetical program that implemented intervention "A" proved to be more cost-effective than the program that implemented intervention "B". However, the cost-effectiveness of mortality reduction does not necessarily mean that it will also be "equitable", as these are two separate dimensions. Deaths can be reduced in a highly cost-effective way when investments are targeting the wealthiest quintiles, just as when they are targeting the poorest. In the former case, the mortality will be reduced, but the inequity will be increased. In the latter, both mortality and inequity will be reduced. We argue that this should be the goal whenever possible, and that a simple check using this framework can help highlight these important issues and enable decision-making that includes this goal. Scaling up health interventions in Q3 will be "equity-neutral", scaling up in Q4 and Q5 will always be "equity-promoting", while scaling up in Q1 and Q2 will be "inequity-promoting"; all three approaches, however, will result in reduction of mortality burden, and in some cases this reduction may even be more cost-effective when interventions are scaled in Q1 and/or Q2, rather than in Q4 an/or Q5.

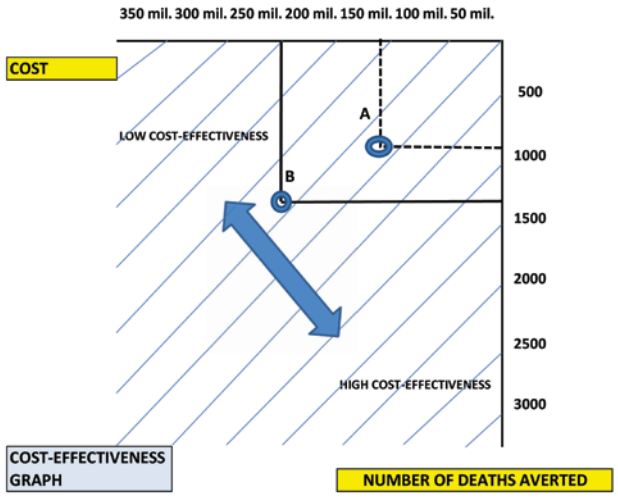


Figure 4 The relationship between the cost of intervention scale-up and number of deaths averted, which determines the cost-effectiveness of the intervention in mortality reduction, presented for each of the five equity strata in the population (Q1 – the wealthiest quintile; Q5 – the poorest quintile).

The complex interplay among factors that influence equity and cost-effectiveness of mortality reduction

If we bring together the previous four graphs into a single decision-making framework, as shown in **Figure 5**, it becomes clear that the relationships between the four determinants (efficiency, effectiveness, impact on mortality and cost-effectiveness) and the impact on equity will not necessarily be intuitive in any setting. The final outcome will be governed by a series of complex and typically nonlinear relationships between the determinants above. Anything that increases the efficiency of delivery (see arrow in the top left quadrant, **Figure 5**), the quality of delivery (see arrow in the top right quadrant, **Figure 5**), and acts upon the greater mortality burden (see arrow in the bottom right quadrant, **Figure 5**) will be more cost-effective (see arrows in the bottom left quadrant, **Figure 5**), and vice versa. Increased efficiency and quality of delivery will tend to make scaling up among the wealthier groups more cost-effective, while the increased size of the burden will tend to make scaling up among the poorer groups more cost-effective (**Figure 5**).

To further illustrate the nature of this complexity, **Figure 5** offers an illustrative example: a fixed sum of money (shown on the "cost" axis) is available to ensure delivery of an entirely new intervention to children in a country. Local policy makers have a choice: if they assume that children in Q1 would find ways to get this intervention anyway, while those in Q5 are arguably too hard to reach, they could invest the available funds to cover as many children in Q2, Q3 or Q4 as possible. The difference is that covering Q2 would increase inequity, while covering Q4 would promote equity and Q3 would be equity-neutral. If similar cost-effectiveness between the three approaches could be demonstrated (in the bottom left quadrant of the proposed framework), then the equity-promoting approach (covering Q4) should be preferred. In this example, implementing the intervention to the children in Q3 is more cost-effective than the other two approaches (**Figure 5**), but the difference is not substantial and covering Q4 could be considered instead.

In the remainder of this paper, we will present and discuss a hypothetical case related to planning of the delivery of an intervention to different equity strata in the population and assessing its cost-effectiveness at different levels of investment.

RESULTS

We will consider a hypothetical case of framework implementation: planning of the delivery of a new intervention, such as vaccine, improved sanitation, or maternal education program, to different social strata in the population and assessing its cost-effectiveness. The upper left quadrant graph in **Figure 6** shows how the level of investment translates to intervention coverage in different equity quintiles in the population of interest (Q1 being the wealthiest and Q5 the poorest). Clearly, in the population of interest an

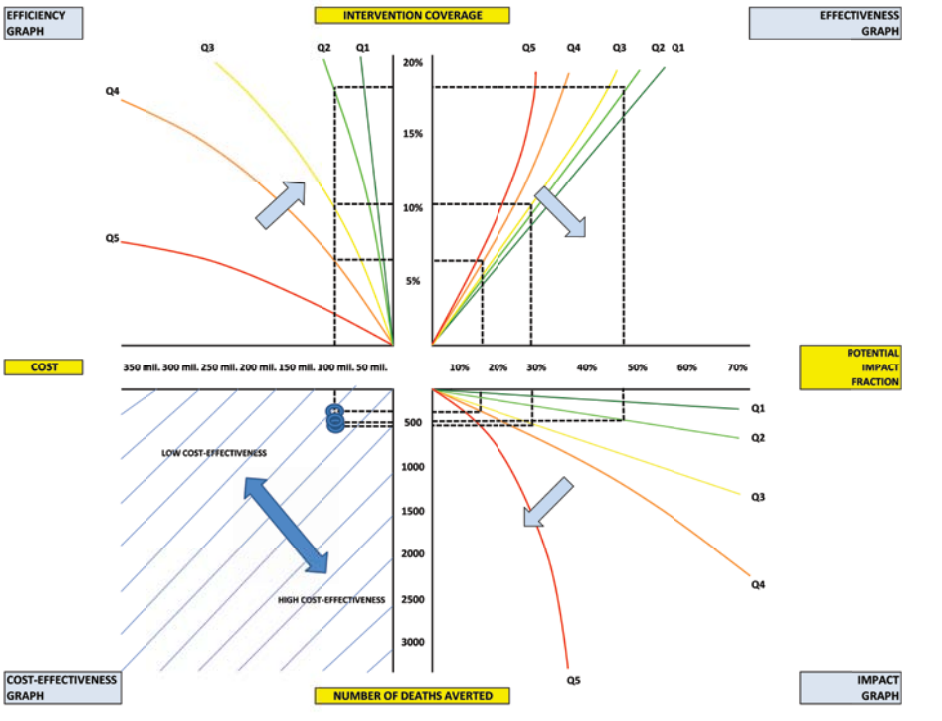


Figure 5 A hypothetical case of planning the delivery of a new intervention to different equity strata in the population (Q2 vs Q3 vs Q4) with a fixed budget and assessing its cost-effectiveness under equity-neutral (Q3), equity-promoting (Q4) or inequitable (Q2) strategy.

investment of US$ 50 million will ensure nearly complete coverage of all 20% children in Q1 quintile, while complete coverage can be achieved with US$ 100 million in Q2. US$ 150 million will cover about 7 out of 10 children in Q3, while US$ 200 million will cover two in three children in Q4. Reaching children in Q5 will be extremely difficult and expensive, and US$ 250 million will only cover about one third of the children in this quintile (**Figure 6**).

The upper right quadrant graph takes into account that the effectiveness of the same intervention will vary in different quintiles. This is because the quality of delivery usually decreases in the poorest equity strata, making the implementation in Q1-Q3 more effective than in Q4-Q5 (**Figure 6**).

The lower right quadrant graph takes into account that the burden of child deaths is not evenly distributed among the five quintiles and it quantifies the number of deaths averted. It is apparent that removing 50% of the mortality burden in Q1 or Q2 removes similar number of deaths (in absolute terms) as preventing 15% of deaths in Q5 (**see Figure 6**).

Finally, the lower left quadrant graph brings the number averted deaths back to the relationship with the initial investment in US$. This allows us to compare many different scenarios and make informed predictions of cost-effectiveness of each scenario relative to alternative ones – all of which would be impossible to predict intuitively. Thanks to graphs in **Figure 6**, we can now conclude that an investment of US$ 50 million in coverage of children in Q1 will be more cost-effective than any of the other four scenarios, with investing US$ 250 million in covering children in Q5 being the least cost-effective. Still, an investment of US$ 150 million in Q5 (denoted as Q5′, follow the parallel dotted lines in **Figure 6**) would be substantially more cost-effective than an investment of US$ 200 million in Q4 or 250 million in Q5. This means that it is, in fact, more cost-effective to invest $ 150 million into the coverage of children in the poorest quintile (Q5′) than it would be to invest $ 250 million into the coverage of children in Q5.

DISCUSSION

The interplay between investments to increase intervention coverage and the "returns" in terms of the number of deaths averted is extremely complex and sometimes counter-intuitive. It is intervention-specific, context-specific, and it depends on several variables that show both linear and nonlinear inter-relationships. All of this should be taken into account when planning investment policies and choosing between the many cost-effective interventions at the national and sub-national level. The lines in the "efficiency", "effectiveness" and "impact" graphs (**Figure 5** and **Figure 6**) necessarily determine the resulting line in the "cost-effectiveness" graph. Any increase in efficiency and quality of intervention delivery, effectiveness of intervention, or burden of disease within any quintile will improve cost-effectiveness. Looking at **Figure 5** and **Figure 6**, shows that any rotation of the lines in the "efficiency", "effectiveness"

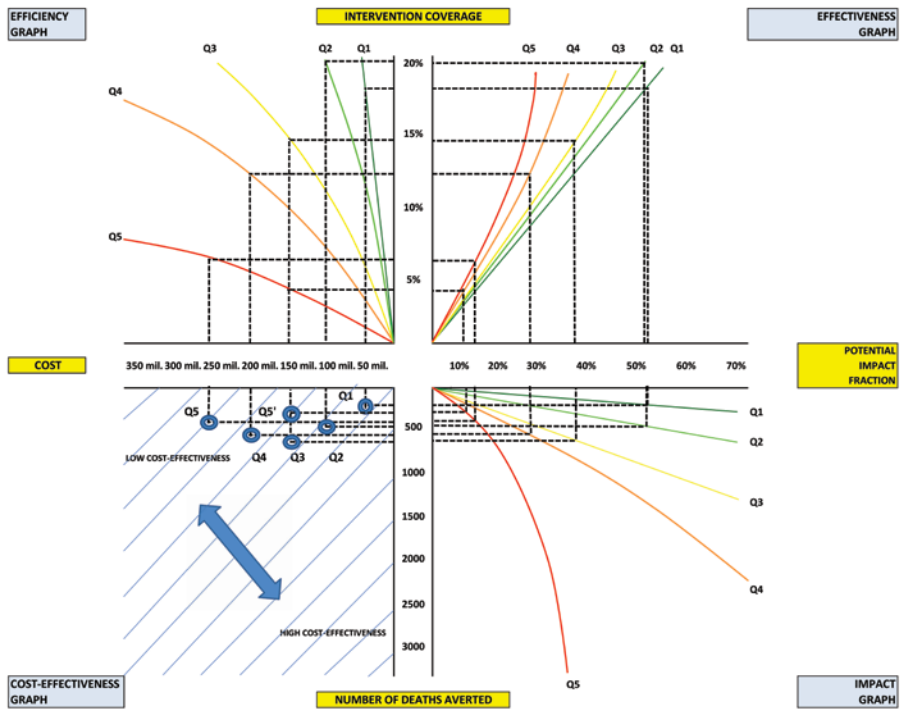


Figure 6 Six hypothetical investment cases of different amounts of funding for scale-up of the same intervention in 5 different equity strata, and with different level of investment into the poorest quintile (Q5).

and "impact" graphs in the clock-wise direction will lead to rotation of the corresponding line in the "cost-effectiveness" graph in the anti-clockwise direction, which is desirable.

Figures 5 and **Figure 6** also expose some unexpected and counter-intuitive properties of this framework. First, when lines anywhere in the graph are located counter-clockwise from the line determined with an equation $x=y$, then the cost-effectiveness will decrease with increasing investment in the same population stratum. This means that smaller investments in the same quintiles may prove to be more cost-effective than larger investments. However, if it is possible to change the slope of the lines through improving contexts, then a scenario may be envisaged in which increasing investments in a population quintile also become increasingly cost-effective. This is particularly important for the poorest quintile, as shown in example in **Figure 6**. The scenario presented in both **Figure 5** and **Figure 6** has also shown that in some contexts the most equitable strategy (ie, investing in the poorest quintiles) is not necessarily the most cost-effective. In this case, the decision-making process becomes really difficult, as it cannot be based on any rational framework, but it rather needs to include value choices. When faced with such an interplay of the key determinants in their particular context, policy makers need to decide whether the majority of the society would value improved equity or cost-effective mortality burden reduction (ie, more deaths averted per money invested, irrespective of the increasing inequity) as the more important goal.

Given the level of general interest in tools that could translate accumulated evidence and information into health policy at the national level, and also in improving equity within low and middle-income countries, there is remarkably little evidence on the differential cost of intervention scale-up, effectiveness of intervention, or the composition of mortality burden by equity strata to support even the most basic analysis. With recent progress in assembling information relevant for international child health policy [1-10], we believe that we will soon begin to have sufficient information to develop a model that could allow early comparative analysis, such as the one described above, at the national level in several representative countries. This model should enable the development of guidelines for prioritizing of interventions in different contexts to maximize the reduction in maternal and child mortality burden relative to the funding available, while taking into account the resulting impact on equity.

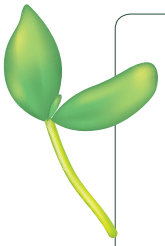
This model should not be considered in isolation from the other worthy and commendable efforts, all of which have "burden of disease/cost effectiveness analysis" as their essential component, such as those promoted by the Disease Control Priorities Project (DCPP) [19]. For example, the Marginal Budgeting for Bottlenecks (MBB) tool was developed by UNICEF and The World Bank [20], WHO-CHOICE (Choosing Interventions that are Cost-Effective) was developed by the World Health Organization [21], and Lives Saved Tool (LiST) developed by Johns Hopkins University scientists and the Futures Institute [22]. The DCPP authors correctly note that factors other than cost-effectiveness influence priority setting in the real world, so the available evidence has to be considered in the context of local realities [12,19]. Both MBB and WHO-CHOICE provide appropriate contextualization tools. However, the LiST software goes further than other existing tools in several dimensions [12]. LiST contains an expansive evidence base of context-specific intervention effectiveness, generated by researchers from the WHO/UNICEF's Child Health Epidemiology Reference Group (CHERG) [23]. It enables estimation of intervention impact on child mortality at national, regional, and global levels [24,25]. Further important advantages of LiST include its validation in both African and South Asian contexts [26], an ability to perform very specific comparisons between alternative investment strategies over a specified time frame in terms of child survival outcomes [24,25], and its attempt to apply an equity lens [27]. However, due to the gap in information on the key determinants of the interplay between cost-effectiveness and equitable impact in maternal and child mortality reduction, none of the present versions of the available tools allow planning of an equitable strategy to reduce maternal and child mortality.

CONCLUSION

In order to assess cost-effectiveness at the national and local level, policy makers would need to know: (i) what is the differential cost of intervention delivery to achieve full coverage in Q1-Q5?; (ii) what is the difference in effectiveness of this new intervention in Q1-Q5?; (iii) what is the difference in mortality burden between Q1-Q5? The interplay among those key determinants needs to be understood, and relative trade-offs need to be quantified before investment decisions can be made. However, in most contexts and for most available interventions there is simply no information on differential cost of scale-up, differential effectiveness and differential mortality burden by equity strata.

We hereby propose a framework that exposes the most important determinants of cost-effectiveness and equitable impact in maternal and child mortality reduction and their interplay. One of the values of this framework is in suggesting how to make interventions delivered to the poorest in the population (Q5) more cost-effective, which is primarily by increasing the efficiency and the quality of intervention delivery, while improving access and promoting care-seeking behaviour and infrastructure to support delivery mechanisms to Q5. The framework also exposes large gaps

in information required to understand the interplay between the key determinants – above all, differential cost of intervention delivery by equity strata; differential effectiveness of intervention by equity strata; and differential size and cause composition of mortality burden by equity strata. Finally, the proposed framework should enable modelling of the "thresholds of cost-effectiveness" for the poorest in the population, by starting the analysis from the bottom-left quadrant ("cost-effectiveness graph") with setting the desired level of cost-effectiveness and, given the burden of mortality, finding the values of effectiveness and cost of scale up that would be required to make the implementation cost-effective while improving equity in the population.



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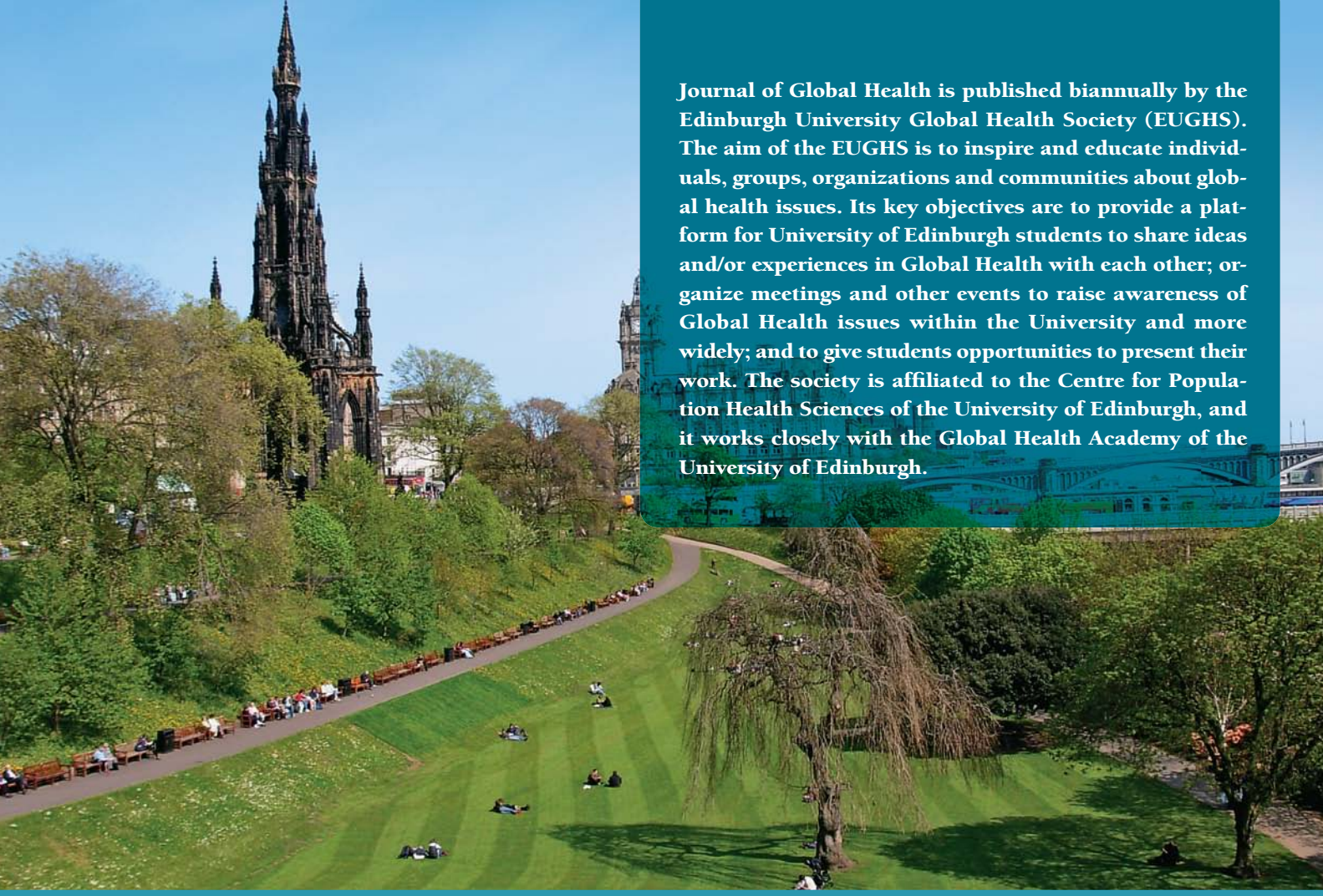

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