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**Scaling up of existing cost-effective interventions could prevent nearly all diarrhoea deaths and about two thirds of pneumonia deaths in children younger than five years in the next decade, if delivered at scale. The cost of such effort was recently estimated at about US$ 7 billion. These activities, along with increased political stability in many low and middle-income countries, their economic development, improved sanitation and access to care, progress in empowering and educating women in the society and strengthening health systems, could all contribute to very substantial reduction of the global burden of child mortality attributable to pneumonia and diarrhoea.**

**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

# Reducing mortality from childhood pneumonia and diarrhoea: The leading priority is also the greatest opportunity

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Pneumonia and diarrhoea have been the leading causes of global child mortality for many decades. The work of Child Health Epidemiology Reference Group (CHERG) has been pivotal in raising awareness that the UN's Millennium Development Goal 4 cannot be achieved without increased focus on preventing and treating the two diseases in low– and middle–income countries. Global Action Plan for Pneumonia (GAPP) and Diarrhoea Global Action Plan (DGAP) groups recently concluded that addressing childhood pneumonia and diarrhoea is not only the leading priority but also the greatest opportunity in global health today: scaling up of existing highly cost–effective interventions could prevent 95% of diarrhoea deaths and 67% of pneumonia deaths in children younger than 5 years by the year 2025. The cost of such effort was estimated at about US$ 6.7 billion.

Pneumonia and diarrhoea have been the leading causes of global child mortality for many decades [1]. Their relative importance in comparison to other causes of child deaths, such as malaria, preterm birth, birth asphyxia, accidents, neonatal infections and cancer, has become fully appreciated in 2003 through the work of the World Health Organization's and UNICEF's Child Health Epidemiology Reference Group (CHERG) [2]. The "Child Survival" series, published by *The Lancet*, has been pivotal in raising awareness that the UN's Millennium Development Goal 4 cannot be achieved without increased focus on preventing and treating childhood infections – particularly pneumonia and diarrhoea – in low– and middle–income countries [3]. The next big step involved the "Global Action Plan for Pneumonia" (GAPP), which summarized the evidence on the epidemiology of acute lower respiratory infections in children, the key etiological agents, the main determinants of the disease, the available and emerging solutions and the main obstacles to their implementation [4]. GAPP's landmark publication in 2008 showed that there are about 156 million new cases of pneumonia each year, and that about one in ten results in a severe episode that requires hospitalization, and a further 10% of severe episodes lead to deaths of affected children [5]. The paper also proposed that *Streptococcus pneumoniae* (SP), *Haemophilus influenzae* type B (Hib), respiratory syncytial virus (RSV) and influenza virus are the pathogens whose interplay is the most likely cause of the large majority of pneumonia deaths in children under five years of age [5]. This led to increased attention to pneumonia prevention through available vaccines against PC, Hib and influenza virus, to complement existing (antibiotic) case management strategies, including those delivered by community health workers. The underdeveloped and weak health systems in low–resource settings, where most deaths occur, cannot easily scale up antibiotic coverage to children who need them most, because of relatively low rates of access to health care [6]. Another obstacle to progress is infrequent care–seeking among parents who did not receive adequate education on this important health issue [6].

Four papers that followed the GAPP initiative, all of them published by The Lancet, have estimated the global and regional burden of SP [7], Hib [8], RSV [9] and influenza [10]. In parallel to understanding the burden of specific

pathogens, new financial mechanisms have been developed – such as the Advance Market Commitment (AMC) – to reduce the prices of available vaccines and deliver them in low– and middle–income countries, where they would otherwise remain unaffordable to local governments [11]. The Global Alliance for Vaccines and Immunization (now called the GAVI Alliance) has been set up to raise funding to purchase these vaccines, with major contributions from the Bill and Melinda Gates Foundation who stood firmly behind the initiative to vaccinate children and prevent respiratory infections [12]. Those efforts ensured that most children in low–resource settings have received Hib vaccination by 2010, and pneumococcal vaccination coverage is also now being scaled up globally [13].

The similar effort for diarrhoea has been lagging behind until recently, when an international collaboration of researchers launched a "Diarrhoea Global Action Plan" (DGAP) [14]. Under the co–ordination of UNICEF, the World Health Organization, and USAID, the initiative has been merged with GAPP into "GAPPD" – "Global Action Plan for Pneumonia and Diarrhoea" [15]. This was a welcome move, because many risk factors are shared between the two diseases, and many approaches to control them could be delivered in parallel through an Integrated Management of Childhood Illness (IMCI) approach. Communities of researchers and policy–makers who are focused on diarrhoea control have also recently acquired the first vaccine effective in preventing an appreciable portion of the burden – rotavirus vaccine [16]. This vaccine will be added to GAVI portfolio to supplement PC and Hib vaccines for pneumonia [17].

The GAPPD group has recently been invited by The Lancet to write a series of papers that jointly address the epidemiology of childhood diarrhoea and pneumonia, the available cost–effective interventions, country–specific challenges and bottlenecks, and suggest policies that could accelerate progress in reduction of global mortality from the two diseases [15,18,19]. The series proposed that scaling up of existing highly cost–effective interventions could prevent 95% of diarrhoea deaths and 67% of pneumonia deaths in children younger than 5 years by the year 2025, if delivered at scale. The cost of this effort was estimated at about US$ 6.7 billion [15,18,19]. These activities, along with increased political stability in many low– and middle–income countries, their economic development, improved sanitation and access to care, progress in empowering and educating women in the society and strengthening health systems, could all contribute to very substantial reduction of the global burden of child mortality attributable to pneumonia and diarrhoea [18,20,21]. We should, therefore, conclude that addressing childhood pneumonia and diarrhoea is not only the leading priority, but also possibly the greatest opportunity in global health today.

There is a growing consensus that an improved understanding of the size of the burden, the leading risk factors and the relative contribution of the leading etiological causes; the available vaccines and other cost–effective interventions, such as community case management with antibiotics, oral rehydration sachets and zinc supplementation; and the momentum that many low– and middle–income countries have gathered in improving their economic outlook, have all provided the international health community with an unprecedented opportunity to substantially reduce the mortality from childhood pneumonia globally over the period of the next decade [15].

To support those ongoing initiatives, several leading medical journals published special issues, or series of articles, focused on childhood diarrhoea and pneumonia (and child survival in general) in the first half of 2013. As noted above, *The Lancet* will publish a four–paper series on childhood diarrhoea and pneumonia in April 2013, which is likely to have very large impact on the field [15,18,19]. *PLoS Medicine* published a PloS Medicine Collection on improving intervention delivery progress tracking and information systems in low–resource settings that could guide policy decisions. BMC Public Health is expected to publish a series of reviews that will present results of meta–analyses of the effectiveness of several key child health interventions, such as breastfeeding and vaccination, which should further strengthen the evidence base for the Lives Saved Tool (LiST) [22]. In this issue, *Journal of Global Health* joins this coordinated international effort launched by the CHERG group. We are bringing together several articles that should fill the remaining gaps in understanding acute respiratory infections and diarrhoeal disease in children. Rudan et al. revise national–level estimates of the morbidity, severe morbidity, mortality, etiology and risk factors for acute lower respiratory infections for 2010 [23]. Fischer–Walker et al. provide an assessment of co–morbidity between childhood pneumonia and diarrhoea [24]. Zwisler et al. use surveys to study the perception and use of oral rehydration sachets, antibiotics, and other therapies for diarrhoea in India and Kenya [25]; Wilson et al. analyse scaling up access to oral rehydration solution for diarrhea, learning from historical experience in low– and high–performing countries [26]; Simpson et al. add to this work by surveying caregivers in Kenya to assess perceptions of zinc as a treatment for diarrhea [27]. Finally, Zipursky et al. report on the global action plan for childhood diarrhea and show how research priorities were developed within this effort [14].

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## CORRECTION

George-Carey R, Adeloye A, Chan KY, Paul A, Kolcic I, Campbell H, Rudan I. An estimate of the prevalence of dementia in Africa: A systematic analysis. *J Glob Health* 2013;2:020401corr1. doi:10.7189/jogh.02.020401corr1

The authors informed the publisher that the term Democratic Republic of Congo (capital: Kinshasa) was used instead of the correct name of the country – Republic of Congo (capital: Brazzaville) in Figure 2, Tables 2 and 3 and the text. The author and the publisher apologise for this error. We have since corrected the online version of the article.

See the original article: George-Carey et al, 2012.

# Africa

Recent statistics on economic growth in Africa have prompted headlines that "Africa is set to become the next big global economic power". However, analysing Africa's development prospects based solely on indicators such as GDP growth rates, per capita incomes, or increase in mobile phone use is misleading. Africa is still deficient in terms of manufacturing. Agriculture and extraction of natural resources are still at the core of most African economies, in contrast to the industrialization that is characteristic of wealthier global economies, such as the USA and China. Indeed, a recent UN report paints a more realistic portrayal of Africa's development prospects, finding that despite some improvements, some African countries are at a standstill in terms of industrialization, with some even moving backwards. Service industries alone cannot, in the long–term, create enough jobs for the millions of African youth; instead, trade arrangements and bilateral agreements should be revised such that Africa is able to adopt sustainable, long–term industrialization policies. (*The Foreign Policy*, 4 Jan 2013)

According to the World Health Organization, the Ministry of Health of Chad has launched an emergency mass–vaccination campaign against yellow fever, following laboratory confirmation of two cases in the country in December 2012. The campaign is supported by the Chad's Ministry of Health, the International Coordinating Group on Yellow Fever Vaccine Provision (YF–ICG11), and GAVI Alliance. (*PANA*, 14 Feb 2013)

Médecins Sans Frontières/Doctors Without Borders (MSF) teams have completed a cholera vaccination campaign in and around the refugee camps in Maban County in South Sudan – a total of 132 500 persons. This action should limit the spread of an outbreak of cholera, but efforts are still required to improve water and sanitation in the camps. With the cooperation of the South Sudan Ministry of Health, MSF launched the vaccination campaign as part of a cholera preparedness and prevention plan. (*MSF,* 24 Feb 2013)

The report by FEWSNET – a famine early warning system – estimated that the famine in Somalia in 2011 may have killed up to 260 000 people, half of them pre–school children. The aid community believes that tens of thousands of people died needlessly because the international community was too slow in their response to hunger in East Africa in late 2010 and early 2011. Previous estimates said that between 50 000 and 100 000 people died in the famine crisis. (*Associated Press*, 29 Apr 2013)

The Democratic Republic of the Congo is the most dangerous place in the world to give birth, with women having one in 30 chance of dying as a result. Finland is the safest, with the risk of one in about 12 000 births. For the past 14 years the "Save the Children" mothers' index records both the risk of maternal mortality and the difficulties women face when they do become mothers. The bottom countries are predominantly in sub–Saharan Africa and they also include Nigeria, Gambia and Somalia, where one in seven children still die before reaching their fifth birthday, compared to one in about 350 in Finland. This year's report presents a separate index on newborn deaths for the first time. It has been noted that the mortality of the children under five years has been steadily decreasing globally in recent years, but there has been little progress on newborns in comparison. (*The Guardian*, 7 May 2013)

# Asia

The polio vaccination campaign in Pakistan faced fresh setbacks when at least 8 health workers were killed in December 2012. Multiple attacks across different locations saw the campaign temporarily suspended. In the past the campaign has faced considerable resistance from the Taliban, who have denounced the vaccination campaign as a cover for espionage. Polio, a highly infectious disease capable of causing permanent paralysis within hours, remains endemic only in Afghanistan, Nigeria and Pakistan. Officials have highlighted the solid gains made against the disease and the potential for polio to be eradicated in Pakistan. The attacks have been condemned by UNICEF, the World Health Organisation, GAVI Alliance and the government of Pakistan. (*GAVI Alliance*, 19 Dec 2012)

World Health Organization warned that the shortage of medicines is becoming critical in Syria, where the conflicts between rebels and government forces persist. Hospitals are in severe need of anaesthesia, antibiotics, serums and other essential medicines, with local pharmacies increasingly unable to provide basic medicines. WHO added that the ongoing conflict continues to impact waste management and the availability of safe water (*UN News*, 1 Feb 2013)

The GAVI Alliance and the Islamic Development Bank (IDB) entered into a partnership with the goal to vaccinate at least 400 million children by 2020 in the bank's member countries. IDB will help GAVI to secure funds for immunization and an estimated US$ 7 billion would be needed to reach its target under the partnership. IDB Chairman Ahmad Mohamed Ali, who signed the memorandum of understanding with GAVI CEO Seth Berkley, said the bank would help select member countries to implement GAVI's vaccination program. (*Devex*, 12 Mar 2013)

A new virus called novel coronavirus (NCoV), which emerged in the Middle East last year killing five people, is adapted to infecting humans but seems treatable with drugs that boost the immune system. The virus is from the same family as the common cold and Severe Acute Respiratory Syndrome (SARS). Up to mid–February there have been 12 confirmed cases worldwide – including in Saudi Arabia, Jordan and Britain. Health officials in the UK found evidence that a new viral illness can spread from person to person. Cases of the infection can mostly be linked to contact with animals, but one person in the UK is thought to have caught the infection from a relative. The new virus is not the same as SARS, but similar to it and also to other coronaviruses found in bats. (*Reuters*, 2 May 2013)

According to Red Cross, health care workers and health institutions came under violent attack in 22 countries last year, in nearly 1000 violent incidents that included 150 killings. Such violence deprived millions of people in need of care. Apart from killings, the incidents include threats and kidnappings. Mr Pierre Gentile, who heads ICRC's "Health Care in Danger" project, said that those figures were just "the tip of the iceberg", because most incidents go unrecorded. (*AFP*, 16 May 2013)

# Australia and Western Pacific

Researchers in Australia have provided a final clue required for developing a new anti–malarial drug, killing the parasite with a salt overdose. The drug could become the first discovery in the fight against malaria in two decades. The malaria parasite survives in red blood cells, which are full of salt, and "...the parasite is quite leaky, but it's got a very effective molecular salt pump, that keeps pushing the salt out again," said Professor Kiaran Kirk, director at the Research School of Biology at Australia National University (ANU). Research teams in the United States and Singapore had developed a drug that attacked the protein that makes up the salt pump, but it wasn't until the ANU researchers tested it that they confirmed it worked effectively. The drug attacks the salt pump and disables it, causing the parasite to fill up with salt and die. Targeting such a basic function is crucial because malaria tends to evolve quickly, developing resistance and rendering other drugs ineffective. (*Reuters*, 19 Feb 2013)

A report released by the Australian National Health Performance Authority (NHPA) showed that the percentage of children fully immunized has dropped to a disturbing level. The data from the Childhood Immunization Register showed that about 8% of Australian children are not fully immunized, and the Australian Medical Association (AMA) warned that the vaccination rate below 93% is unsafe for protecting the children and the community. AMA's President, Dr Steve Hambleton, called this situation "really disturbing". The vaccination rate dropped both in low and high socio–demographic areas. (*Xinhua*, 11 Apr 2013)

The HPV vaccination of young girls is showing successes in Australia. A study that compared rates of HPV–related diseases in the three years before the vaccine program and in the four years afterward in 86 000 persons showed a 93% decrease in genital warts in young women, although only 85% were vaccinated. This suggests that the herd immunity is protecting both young men and, in turn, unvaccinated women. (*New York Times*, 19 Apr 2013)

Mr Bill Gates urged Prime Minister Julia Gillard to spend more foreign aid money on tackling malaria and polio during his visit to Australia in May this year. Mr Gates, who resigned from running Microsoft in 2009 to work full–time on his philanthropic activities, has steadily remained a driving force behind the GAVI Foundation, which has pledged to immunize 150 million people by 2015 in one of the largest population health projects that have ever been undertaken. (*news.com.au*, 7 May 2013)

The Australian Government will increase its official development assistance to a record US$ 5.7 billion in 2013/14, an increase of approximately US$ 500 million (or 9.6%) on 2012/13, bringing the aid budget to 0.37% of gross national income (GNI). This will be the highest aid budget in Australian history, at a time when aid among OECD countries has fallen by 4% in real terms. Australia's aim is to continue to increase its donations to 0.5% of GNI, deferring this target by one year – to 2017/18. (*Australian Minister for Foreign Affairs*, 13 May 2013)

# China

Within the first week into his tenure as China's new president, Mr Xi Jinping already stressed his country's strong and continuously growing ties to the African continent and the connected future of the world's two developing economies. In recent years, China has played a major role in development of parts of sub–Saharan Africa and its economic importance in African region is steadily growing. (*Christian Science Monitor*, 19 Mar 2013)

This year, 32 years since China's National Population and Family Planning Commission (NPFPC) was established to oversee the world's largest, longest–standing population control programme – the "one child policy" – the country's leaders announced plans to dissolve it into the Ministry of Health. The National People's Congress approved the proposal in March this year, and the commission ceased to exist, leaving the future of the country's fertility policy in doubt. The "one–child policy" limited most Chinese families to a single child, and those in rural areas or those qualifying for other exceptions, to two, preventing more than 400 million births according to China's national statistics. Financial Times reported that in the past 40 years Chinese doctors have performed more than 300 million abortions and about 200 million sterilisations. Many observers forecast a change in China's fertility policy this year following the country's once–in–a–decade leadership transition. For years, economists and demographers have argued that by constraining the size of the next generation, the country's fertility policy has contributed to a grave demographic imbalance that could emerge in the coming decades, as the country's elderly outstrip its labour force. (*The Lancet*, 23 Mar 2013)

China's "black clinics" are flourishing in big cities, as government debates health reform. Usually arranged as one–room shacks with a single light bulb on side streets, they provide the sole source of medical care for a growing population of migrant workers who are not recognized as city residents and do not qualify for cheaper healthcare at government hospitals. For many millions of migrant workers, whose hometowns are too far away to provide medical subsidizes, an unregulated world of back ally "black clinics" is the only option available. As the China's economic growth depends on those workers, the two–tier nature of China's overburdened health care system is beginning to appear inadequate to address this problem. A reform of the contentious "hukou" system of household registration may be required, although the system has been a cornerstone of government policy for decades. Dating back to 1958, the "hukou" system has split China's 1.3 billion people along urban–rural lines. This prevented many of the about 800 million Chinese, registered as rural residents, from settling in cities and taking advantage of urban welfare and services. China's new government is considering a change in this divisive system. (*Reuters*, 27 Mar 2013)

The Health Effects Institute in Boston reported that more than 1 million people are dying prematurely every year from air pollution in China and presented their findings in Beijing. On many days in many cities, the air in China is thick with smog, with people commonly walking the streets wearing masks. It is now estimated that in China, approximately 1.2 million people die prematurely from exposure to outdoor air pollution, with about two–thirds of all the deaths now occurring in Asia. Air pollution has become the fourth leading cause of death in China, mainly affecting frail populations, such as people with asthma and the very young children who live in highly polluted areas. (*NPR*, 02 Apr 2013)

The new H7N9 strain of the flu virus, first discovered in humans in March, has now killed at least 24 people. Cases of the virus were confirmed in more than 100 people and have spread to several new provinces in recent days, including Fujian and Hunan. In April, a man in Taiwan became the first case of the flu outside mainland China, having caught the flu while travelling in China. The World Health Organization has called the virus "one of the most lethal" and said that it was more easily transmitted than an earlier strain that has killed hundreds since 2003. Chinese scientists have confirmed that the bird flu strain has been transmitted to humans from chickens, but officials say there is no evidence yet of human–to–human transmission. (*Reuters*, 30 Apr 2013)

# Europe

The debt crisis of the Euro zone continues, while austerity policies maintain the recession, according to an annual UN report. A press release, that announced the "World Economic Situation and Prospects 2013" report, produced by the UN Department of Economic and Social Development (DESA), the UN Conference for Trade and Develop-

ment (UNCTAD) and UN regional commissions, highlighted that at least five economies are in recession, with very poor prospects for the Europe's mid–term economic future. (*UN News*, 17 Jan 2013)

▸▸ Approximately 800 children in Europe have developed narcolepsy, a chronic incurable sleep disorder, after immunization with the H1N1 swine flu vaccine Pandemrix, manufactured by GlaxoSmithKline. Independent peer–reviewed studies in Scandinavia, Ireland, France and more recently in the UK demonstrate spikes in narcolepsy cases. The UK study published in the *BMJ* suggested a risk narcolepsy following Pandemrix vaccination of around one in every 55 000 doses. However, the lead author, Professor Liz Miller said: "Long term follow up of people exposed to Pandemrix is needed before we can fully establish the extent of the association." (*Reuters*, 22 Jan 2013)

▸▸ At the World Economic Forum in Davos it has been announced that Germany agreed to provide 1 billion Euros to the Global Fund to Fight AIDS, Tuberculosis and Malaria, according to Germany's Minister for economic cooperation and development, Mr Dirk Niebel. (*CNN*, 24 Jan 2013)

▸▸ Health officials in the UK said that a measles epidemic is "spreading at an alarming rate across areas of Wales". The warning came as latest figures showed the number of cases in the Swansea area to more than double in less than a month, to 432 cases in total, of which 51 have been hospitalised. They added that, if the numbers of parents bringing their children for MMR jabs does not dramatically increase, measles will continue to spread, predicting that the outbreak could result in about 1000 cases. (*BBC*, 26 Mar 2013)

▸▸ French Health Ministry said that France has identified its first case of a new strain of coronavirus, emerging from the Middle East, in a person recently returned from a stay in the United Arab Emirates. The virus came to scientists' attention in September 2012. Since then, there have been at least 30 laboratory–confirmed infections with the virus globally, including 18 deaths, according to the World Health Organization. (*Reuters*, 8 May 2013)

# India

▸▸ Recent advances in Chinese vaccine manufacturing are beginning to threaten India's supremacy in this market. Currently, India produces 40–70% of the World Health Organization's demand for DPT and BCG vaccines and 90% of measles vaccines, exporting them to 150 countries. Mr PV Appaji, Director General of the Pharmaceuticals Export Promotion Council of India stated that the government should come forward to help Indian vaccine makers with capacity building by offering funds at affordable interest rates, adequate power supply and infrastructure. He added that new export markets for Indian pharmaceutical industry were being identified, including Latin America and Africa, and that Indian pharmaceutical export target of US$ 25 billion by 2014 had now been revised to 2015 due to weak international economic situation. (*Times of India*, 20 Dec 2012)

▸▸ In January 2013, the Indian government launched an innovative direct cash transfer program that deposits government pension and scholarship payments directly into recipients' bank accounts. Despite being currently operative in only 20 districts, the program is seen as a leap forward for India's antipoverty agenda, as the current practices often inadvertently result in feeding corrupt intermediaries instead of intended recipients. However, critics assert that the program is simply a political ploy to buy the votes of the poor, and that in a country where millions do not even have access to banks, direct money transfers are only a minor aspect of a much greater effort needed to permanently lift people out of poverty. This includes provision of better schools, hospitals and shops. (*New York Times*, 05 Jan 2013)

▸▸ There are Indians who welcome the end of British aid for India, announced for 2015, on grounds of national pride. However, Amanda Glassman, director of global health policy at the US–based Centre for Global Development, acknowledged that British aid for India was small in absolute terms, but said it could still make a big difference, especially in India's poorest states where only 44% of children under five are fully vaccinated. (*The Guardian*, 18 Feb 2013)

▸▸ India's Supreme Court rejected Novartis AG's attempt to patent a new version of a cancer drug in a landmark decision. Novartis argued it needed a patent to protect its investment in *Glivec* (imatinib), used in treating chronic myeloid leukaemia and other cancers. However, campaigners argued that the company was trying to use loopholes to make more money out of a drug whose patent had expired. This decision sets a precedent that will prevent international pharmaceutical companies from obtaining fresh patents on updated drugs which makes them unaffordable for most

of India's 1.2 billion population, where 40% earn less than US$ 1.25 a day. Healthcare activists claim that this will ensure that poor patients around the world would continue to get access to cheap generic versions of the lifesaving medication. *Glivec* costs about US$ 2600 a month, whilst the generic version in India costs US$ 175 a month. The generic version produced in India makes it accessible to poor not just in India, but also across the world. (*The Guardian*, 1 Apr 2013)

▸▸ Indian Department of Biotechnology plans to build on the success of the public–private partnership that led to the development of the first indigenous rotavirus vaccine to combat childhood diarrhoea. The Department announced its ambition to shift its target towards studying vaccines for dengue, tuberculosis and malaria, with a particular focus on affordability. The Department will readily co–operate with the pharmaceutical industry in the development of future vaccines. (*The Hindu*, 16 May 2013)

# The Americas

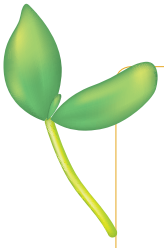
▸▸ The international response to the earthquake in Haiti was overwhelming: more than US$ 9 billion was raised from public and private donors. Official bilateral and multilateral donors pledged as much as US$ 13 billion and almost 50% of these pledges have been disbursed, according to UN sources, while private donations added further US$ 3 billion. However, three years after the tragedy it is not really clear how the money was spent or whether the desired outcomes were achieved. (*The Guardian*, 14 Jan 2013)

▸▸ Leaving the post of the US secretary of state, Ms Hillary Rodham Clinton will be remembered for not concentrating on long–term intractable conflicts, but rather focusing on more feasible international development goals: saving children from dying of preventable diseases, connecting poor farmers to markets as part of a new food security program, and improving the prospects for women who lack of education and resources. During her tenure, she became an icon of global development. (*Devex*, 31 Jan 2013)

▸▸ GlaxoSmithKline Plc (GSK) and the Texas A&M University System won approval from the US Health and Human Services Department for a US$ 91 million flu vaccine plant. The facility would be able to produce treatments in response to pandemics or biological attacks. It should be located in the College Station, Texas, northwest of Houston, creating jobs for up to 300 people directly, but up to 7000 further indirect and related jobs. (*Bloomberg*, 26 Mar 2013)

▸▸ The joint study between United Nations Children's Fund (UNICEF) and the Mexican Government reported that more than 20 million children and adolescents in Mexico are estimated to live in poverty, with five million in extreme poverty. The UNICEF Representative in Mexico, Ms Isabel Crowley, said that although the economy has grown well in Mexico, this does not always mean that the poor are better off, because human development indexes in parts of Mexico are close to those of some of the world's least developed countries. Moreover, children are overrepresented among the poor. In 2010, 46% of all Mexico's residents lived in poverty, but in children the poverty rate rises to 54%. The study also reported that nearly 14% of Mexican pre–school children are stunted, ie, slowed in their development, which is often a result of malnutrition. The rate is higher in rural areas, reaching nearly 33% among indigenous children. (*UN News*, 3 Apr 2013)

▸▸ The Information Technology and Innovation Foundation (ITIF), a US–based think tank, recommended that the Congress should suspend trade benefits for India. This comes as a result of growing unease in the US over Indian policies that block American exports, and their exploitation of costly US research to develop new medicines and other forms of valuable intellectual property. The US House of Representatives' Ways and Means Committee recently held a hearing on this topic, where a larger number of complaints were made about India's industrial policies. ITIF listed actions and policies taken by the Indian government that were "stripping" foreign biopharmaceutical companies of valuable patent protections. (*Reuters*, 14 May 2013)



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# The Bill and Melinda Gates Foundation

In his annual letter for 2013, Mr Bill Gates emphasized the importance of measurement to improving the human condition. He reflected upon the agreement signed in 2000 by the United Nations "...as one of the greatest successes in terms of using measurement to drive global change". The Millennium Development Goals, supported by 189 nations, specified the year 2015 as a deadline for making measurable improvements across a set of crucial areas that included income, health and education. As an example, the concrete goal of reducing child mortality by two–thirds created a clear target by which to measure success or failure; and regular assessment of the progress, followed by further improvements, are important means to achieving such global targets, to which political commitment was made. (*Wall Street Journal*, 25 Jan 2013)

In a joint statement released by the Bill & Melinda Gates Foundation and the Carlos Slim Foundation, the two of the world's wealthiest persons, Mr Bill Gates and Mr Carlos Slim, said that they planned to use their foundations' resources to promote research and the development of agricultural technology. This should increase farmers' productivity and reduce hunger among the world's poor people. (*Forbes*, 13 Feb 2013)

During his visit to Ghana in March 2013, Mr Bill Gates reinforced his belief that the world must commit to wiping out the remaining cases of polio and finally eradicate the disease, despite squeezed aid budgets and violence that has been plaguing vaccination efforts in a few remaining endemic areas. In April, he announced in Abu Dhabi that his foundation will contribute US$ 1.8 billion to the Global Polio Eradication Initiative, a third of the total funds needed. (*AFP*, 26 Mar 2013)

In March this year, the Department of Biotechnology (DBT) of India, its Biotechnology Industry Research Assistance Council (BIRAC), and the Bill & Melinda Gates Foundation launched "Grand Challenges India". Through this partnership, the government and the foundation will co–fund projects that aim to harness Indian innovation and research to develop affordable and sustainable solutions that could improve health in India and around the world. Under the Memorandum of Understanding, signed last year, the DBT and the Gates Foundation have agreed to invest up to US$ 25 million each over five years in innovations in vaccines, drugs, agricultural products, and interventions related to malnutrition, family and child health. DBT and BIRAC join a global network of the Grand Challenges framework, along with USAID, Grand Challenges Canada, and Grand Challenges Brazil. They are all committed to seeking out and rewarding not only established researchers in science and technology, but also young investigators, entrepreneurs, and other innovators to help expand the pipeline of ideas to fight major global health problems. (*BMGF*, 04 Apr 2013)

Five Japan–based pharmaceutical companies announced that they would be forming a public–private partnership with the Japanese government. The new fund, called the "Global Health Innovative Technology" (GHIT), should assist low and middle–income countries in their fight against infectious diseases. The fund will be composed of Takeda, Astellas, Daiichi–Sankyo, Eisai and Shionogi, also including the Bill & Melinda Gates Foundation and the Japanese government. They will be developing medicines, vaccines and diagnostics for poor countries. (*Japan Daily*, 8 Apr 2013)

# The GAVI Alliance

In December 2012, the GAVI Alliance, in an unprecedented move, partnered up with communications giant *Vodafone* in a bid to increase vaccination rates in developing countries of Africa. The three–year partnership, making Vodafone the eighth member of the GAVI alliance, will aim to establish mobile technology as a primary means of surveillance and tracking in terms of vaccination. Some ways in which the system would operate include reminding mothers of their child's vaccination by text messages, enabling appointments to be made through telephones, enabling health workers to access patients' health records through their phones, and monitoring stocks to ensure availability. This initiative will help GAVI achieve its aim of vaccinating a quarter of a billion more children by 2015. A pilot project is currently being set up in Mozambique. (*The Guardian*, 18 Dec 2012)

The GAVI Alliance and its partners plan to support rotavirus vaccination in at least 40 countries, covering 50 million children by this life–saving intervention by the end of 2015. In 2006, the first countries to receive GAVI rota-

virus funding were mainly in Latin America. The support will now be extended to additional states, including 16 African countries, where more than 50% of all rotavirus deaths occur. Rotavirus is the leading cause of life–threatening diarrhoeal disease and it is estimated to cause nearly half a million deaths each year. (*Vaccine News Daily*, 18 Dec 2012)

▸▸Following the reports that approximately 800 children in Europe have developed narcolepsy after immunization with the H1N1 swine flu vaccine Pandemrix, manufactured by GlaxoSmithKline, the use of Pandemrix has been restricted since July 2011 in people under the age of 20 across Europe. Understandably, experts from both pharmaceutical industry and academia are wary to confirm causal link before more evidence is obtained, because rare adverse reactions can quickly develop into vaccine scares that spiral out of all proportion. (*Reuters*, 22 Jan 2013)

▸▸GSK plans to form a joint venture in India to produce a six–in–one vaccine that will protect children in poor against infectious diseases including polio. A 50–50 venture with India's Biological E Ltd should develop a vaccine that would combine Glaxo's injectable polio shot with a vaccine produced by Biological E that protects against five diseases, including diphtheria and tetanus. The joint venture will cover the development costs for the candidate vaccine, with subsequent development costs split equally. (*Bloomberg*, 28 Jan 2013)

▸▸The GAVI Alliance aims to protect more than 180 000 girls in eight African and Asian countries from cervical cancer by funding immunization projects with vaccines from *Merck* and *GlaxoSmithKline*. Ghana, Kenya, Laos, Madagascar, Malawi, Niger, Sierra Leone and Tanzania should be the first countries to receive support for cervical cancer protection pilot projects. (*Reuters*, 03 Feb 2013)

# The World Bank

▸▸ Dr Timothy G. Evans has been appointed as the World Bank's new Director for Health, Nutrition and Population. Dr Evans is currently the Dean of the James P. Grant School of Public Health of BRAC University in Bangladesh; he previously served as Assistant Director General at the World Health Organization, heading the Evidence, Information, Research and Policy Clusters, where he oversaw the production of the annual World Health Report. Dr Evans is well known as a leader in advancing global health equity and health systems performance, through his work with the Rockefeller Foundation and the Harvard School of Public Health. He also contributed to the development of innovative partnerships, including the GAVI Alliance, INDEPTH and Health Metrics Networks, the Global Health Workforce Alliance and the World Alliance for Patient Safety. He earned his DPhil in agricultural economics at Oxford, and pursued medical and postgraduate studies at McMaster and Harvard Universities. (*The World Bank*, 28 Jan 2013)

▸▸ Development assistance for health increased only by 2.5% (to US$ 28.1 billion) in 2012, after expanding at an average growth rate of 11% per year between 2001 to 2010, according to a report by the Institute for Health Metrics and Evaluation (IHME). Increased spending by the GAVI Alliance and UNICEF made up for lower contributions from the US, France and Germany. Governmental contributions dropped 4.4% – the US cuts were 3.3%, France's 13.0% and Germany's 9.1%, while UK and Australia were the only two nations among the six largest bilateral donors that increased funding. (*Bloomberg*, 6 Feb 2013)

▸▸ In 2012, the World Health Assembly endorsed a new health goal: to reduce avoidable mortality from non–communicable diseases (NCDs) by 25% by 2025 (the "25 by 25" goal). Although clearly trying to keep the momentum after the UN General Assembly's political declaration on the prevention and control of NCDs in 2011, the obstacles to achieving this goal are great and largely under–studied, because they are highly politically sensitive. Today, chronic NCDs remain the least recognised group of conditions that threaten the future of human health. (*The Lancet*, 12 Feb 2013)

▸▸ International aid for health is measured in billions of dollars, but it is still only a fraction of what most recipient country governments need to spend on health care for their people. In 2010, India received US$ 775 million in development assistance in health (DAH). This amount included financial DAH from the World Bank (IDA and IBRD), Asian Development Bank, African Development Bank, Inter–American Development Bank, Global Fund to Fight AIDS, Tuberculosis and Malaria, the GAVI Alliance, and the Bill and Melinda Gates Foundation. However, this amount was just 1.6% of what the both central government and state governments spent jointly on public health. (*Times of India*, 25 Feb 2013)

▸▸ The biggest emerging markets are uniting to tackle under–development and currency volatility. During an an-

nual summit in Durban, South Africa, they discussed plans to set up institutions that could challenge the current roles of the World Bank and International Monetary Fund. The leaders of the BRICS nations – Brazil, Russia, India, China and South Africa – are set to establish a new development bank. They also discussed generating foreign–currency reserves to help them buffer the balance of payments or currency crises. The BRICS nations, with combined foreign–currency reserves of US$ 4.4 trillion and 43% of the world's population, are seeking greater influence in global finance to match their growing economic power. They have already called for an overhaul of the leadership of the World Bank and IMF, which were created in Bretton Woods, New Hampshire, in 1944, and they oppose the practice of the respective presidents being drawn from the US and Europe. (*Bloomberg*, 26 Mar 2013)



# United Nations (UN)

For the first time in almost five years, the UN Secretary–General Ban Ki–moon returned to his own office. He expressed enthusiasm for the renovated Secretariat building, said to be one of the cleanest and most eco–friendly buildings in the world. The original had long been known to lack the standards expected of modern buildings, with water leakages, asbestos and poor ventilation systems. The renovation project, worth US$ 2 billion, has ensured improved safety, accessibility and environmental performance. The building, in its landmark site over the East River in Manhattan, has maintained its original iconic façade and is one of several buildings undergoing changes. Mr. Ban stated his belief that in their new headquarters the UN could "better serve the world's people". (*UN News*, 17 Dec 2012)

The World Trade Organisation is seeking a new leader to take the helm at the world's leading trade body, as the current leader Pascal Lamy steps down in August 2013. The long selection process has already shortlisted nine candidates, five of them from emerging economies around the world. The changes expected from the new Director–General could have a huge impact on the WTO, which has been struggling in a recent financial climate. The work of the WTO was once crucial in building trade capacity and negotiating trade deals, but in recent times it spends an increasing amount of time settling disputes. Moreover, it has often been criticised for not making trade fair and accessible for emerging economies. (*The Guardian*, 13 Jan 2013)

A recent poll carried out by the Better World Campaign showed that around 8 out of 10 voters believe it is in America's best interests to continue to actively support the United Nations, with voters of all political parties recognising the contemporary relevance of the United Nations. When asked specifically about the World Health Organisation, voters overwhelmingly voted that it was important for the US to remain a member. The results showed that very few voters would support a cut in international aid and development funding, contrary to proposals put forth by members of the congress. These findings, alongside many others in the report, have important implications for US politicians by clarifying voter opinion on spending and America's global involvement. (*UN Dispatch*, 16 Jan 2013)

The exodus of Syrians fleeing two years of violent conflicts increased the number of refugees in neighbouring countries to more than a million, according to the United Nations Refugee Agency. The number has increased by around 420 000 this year, with around 7000 to 8000 Syrians leaving the country daily. More than half of them are children under the age of 11. Millions more people are displaced internally. The United Nations High Commissioner for Refugees, António Guterres, warned that the international humanitarian response is dangerously stretched. Around 330 000 Syrians have sought shelter in Lebanon, 320 000 in Jordan, 185 000 in Turkey, 105 000 in Iraq, 43 500 in Egypt and around 8000 across North Africa, with others having fled to Europe. (*New York Times*, 06 Mar 2013)

The UN's latest development report stated that poverty reduction in the developing world was exceeding all expectations. The report quotes an "epochal global rebalancing", in which higher growth rates in at least 40 poor countries are presently helping to lift hundreds of millions out of poverty and into a new "global middle class". According to the report, "never in history have the living conditions and prospects of so many people changed so dramatically and so fast". The report explains that the brighter global picture is the result of "international and national aid and development projects, investing in schools, health clinics, housing, infrastructure and improved access to water". The UN also pointed to trade as being a key factor, presently improving conditions in Afghanistan, Ethiopia, Rwanda and Sierra Leone. These improvements have not been measured in the past, when poverty has only been defined in income terms, without taking into account health, education and living standards. The new measure – the Multidimensional Poverty Index (MPI) – includes ten indicators to calculate poverty: nutrition, child mortality, years of schooling and attendance, cooking fuel, water, sanitation, electricity assets and a covered floor. (*The Guardian*, 17 Mar 2013)

# UN AIDS AND THE GLOBAL FUND

At the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), the AIDS expert Dr Mark Dybul has been appointed as the new Executive Director. Mr Dybul helped found and later managed the implementation of the President's Emergency Plan for AIDS Relief (PEPFAR) from 2006 to 2009. His term follows a global financial crisis and a managerial turmoil at the organization, as several donors ended their contributions, while uncertainties due to corruption charges continue. (*Lancet Infectious Diseases*, 7 Jan 2013)

A child in Mississippi was reported "cured" of HIV. Doctors treating the two and a half year old said that a "functional cure" meant that they tested negative for the virus, although it was expected to still be present in small concentrations in her body. The child stopped receiving care one year previously. She had received intensive treatment with three antiretroviral medications 30 hours after birth, which made the child's viral load undetectable within a month. Moreover, a report has emerged from the Pasteur Institute in Paris regarding 70 adults who received early multi–therapy ART, which was continued for an average of three years before treatment was disrupted; fifteen of those patients now have no traces of HIV in their blood. It appears that early and intensive treatment limits the infection of CD4 cells and therefore reduces HIV's ability to persist in the body, preserves the immune response and reduces the diversity of the virus, all of which appear to facilitate control of the virus. Although this progress received massive media attention, it offers little to the majority of HIV sufferers, as it is rare for the virus to be detected at such an early stage. (*UNAIDS*, 04 Mar 2013)

Health leaders from Africa and international agencies gathered in Swaziland to launch a new initiative against tuberculosis (TB), including TB among people living with HIV. Backed by several new investments worth more than US$ 120 million, the leaders signed the "Swaziland Statement". This document commits them to accelerate progress against the two diseases in the next 1000 days. They should also work with Southern African Development Community (SADC) countries to achieve the international targets of cutting deaths from TB and HIV–associated TB by half by 2015, in comparison to 1990 levels. (*The Global Fund/ReliefWeb*, 20 Mar 2013)

The latest reports on AIDS in sub–Saharan Africa, the epidemic's long–term epicentre, are bringing good news. New HIV infections have declined by 25% since 2001, with AIDS–related deaths decreasing by 32% over the past 6 years, with expanded options for testing and treatment. After decades of pessimistic news about AIDS in Africa, there is more optimism about the control of the pandemic. Most of the measured improvements in AIDS in Africa resulted from cumulative, widespread behaviour change that reduced new HIV infections. (*Slate*, 28 Mar 2013)

The Global Fund to Fight AIDS, Tuberculosis and Malaria has set the target of raising US$ 15 billion to help countries fight the three infectious diseases in the 2014–2016 period. The majority of the funds are likely to come from governments of the United States, France, Britain, Germany and Japan, ie, the five largest donors to the Global Fund. The Global Fund's assessment report indicates that a total need of US$ 87 billion is forecast for 2014–2016 period for their HIV/AIDS, tuberculosis and malaria programs world–wide. (*Xinhua*, 9 Apr 2013)

# UNICEF

In December 2012, the latest report from Multilateral Organisation Performance Assessment Network (MOPAN) was released. Formed in 2012, this association of seventeen countries aims to assess organisational effectiveness of multilateral organisations. The evaluation, which was lead by donor countries Austria and Spain, found that UNICEF has made remarkable strategic improvements in the past three years. This assessment was based on a survey completed by individuals from MOPAN donor governments, national partners and peer organisations. They indicated that UNICEF's greatest strength is strong working relationship with its partners, followed by its technical expertise and credibility, significant field presence and close proximity to local actors on the ground. A particular area requiring improvement was heavy and inflexible administrative processes, including slow release of funds to partners. The next MOPAN report is expected in 2015. (*UNICEF*, 31 Dec 2012)

The births of nearly half the world's children are not registered, which leaves them outside support and protection systems and uncounted in policy decisions. UNICEF supports the right of every child to be registered at birth, without discrimination, which is a critical first step towards safeguarding child's lifelong protection – by establishing an official identity, a recognized name and a nation-

ality. However, 49% of children under the age of 5 are not registered world–wide. Children with no birth certificate don't exist before the law, and are in danger of remaining on the margins of society, facing major challenges in accessing health care, education and social assistance. (*UNICEF*, 12 Feb 2013)

The United Nations Children's Fund (UNICEF) announced that more than a quarter of children under the age of 5 worldwide are permanently "stunted" from malnutrition, leaving them physically and intellectually weak. This represents an unacceptable waste of human potential. Mr Anthony Lake, UNICEF's Executive Director, said that organized provision of vitamins and clean water and a focus on breastfeeding from birth could have helped some 165 million children to achieve normal development. However, their lack of proper nutrition makes them increasingly vulnerable to illness and premature death. The countries with the highest levels of stunted children are concentrated in sub–Saharan Africa and South Asia. (*Associated Press*, 15 Apr 2013)

UNICEF has warned that it would become unable to provide "life–saving" aid to Syrian refugees in Jordan and other countries due to shortage of funds. The demands related to the conflicts in Syria are rising exponentially, and Ms Marixie Mercado, a spokeswoman for UNICEF, declared the agency "broke" in terms of their capacity to continue to support the refugees. (*BBC News*, 5 April 2013)

According to UNICEF, WHO and USAID, child deaths from pneumonia and diarrhoea could be virtually eliminated by 2025. The new plan seeks an "integrated approach", starting with standard ways to protect children from infections, but also adding the newer vaccines against pneumococcal bacteria and rotavirus. Dr Elizabeth Mason, the Director of Maternal, Newborn, Child and Adolescent Health at the WHO, said that the amount required to achieve this would be just over US$ 6 billion to 2025. These funds could come from national health budgets, better use of existing funds, and partners, such as the GAVI Alliance. A successful effort against the biggest killers of children will require co–ordinated effort in 15 interventions, from clean water and antibiotics to vaccines. (*Reuters*, 12 Apr 2013)

# World Health Organization (WHO)

The World Health Organisation (WHO) has recently qualified dengue as the fastest–spreading tropical disease today. The organisation estimates that 50 million cases occur annually, but recent research suggests that the actual numbers may be twice as much. The disease, spread principally by the mosquito *Aedes aegypti*, is now present on every continent. Europe suffered its first outbreak since the 1920s in 2012, with about two thousand people affected in Spain. A specialist at the WHO's control of neglected tropical diseases department said that the mosquitoes most probably reached Europe through the importation of ornamental bamboos and second–hand tyres. Although vector control strategies have been put in place in seaports and airports, it can be quite difficult to detect mosquito eggs. With such a quick dissemination, it is not unlikely that the world may face a dengue pandemic in the future. Vaccines against dengue are still largely in the experimental stages and the most advanced one, developed by Sanofi, proved to be effective only in 30% of cases in a clinical trial. (*Reuters*, 16 Jan 2013)

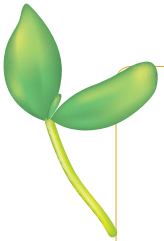
Dr Hiroshi Nakajima, a Japanese physician who led the World Health Organization from 1988 to 1998, has died in Poitiers, France, at the age of 84. The Western nations twice opposed his election as director general, arguing that he had not infused the agency with a clear sense of direction, and had let its budget and bureaucracy increase far beyond reasonable need. (*New York Times*, 28 Jan 2013)

For the first time, the three international organizations focused on health, intellectual property and trade – WHO, WIPO, WTO – have pooled their expertise on a study of policies needed to advance medical and health technologies and to ensure they reach the people who need them. Mr Greg Perry, executive director of the Medicines Patent Pool, said that their joint report "...adds further weight to the idea of public–health oriented licensing as a key win for all stakeholders in the public health arena: from pharmaceutical companies, to generic companies, to – most importantly – people living with HIV". (*WHO*, 5 Feb 2013)

The global development assistance for health (DAH) has increased by nearly 500% in the last two decades, but the funds disbursed through the World Health Organisation (WHO) increased by only 62%. The WHO's share of the global DAH fell from 25% to only 9% between 1990 and 2010, as revealed in a paper published in the *The Lancet* and authored by several employees of the WHO. The channelling of available resources through many new big players in global health has raised questions about the focus of health spending and the role of WHO.

WHO's core budget is still mainly intended for providing leadership on crucial health issues, shaping the research agenda, setting norms and standards, promoting and monitoring implementation and assessing health trends. (*Times of India*, 11 Feb 2013)

▸▸ The Global Vaccine Action Plan (GVAP) for the period 2011–2020 has been endorsed by the 194 Member States of the World Health Assembly in May 2012. GVAP is a roadmap to prevent millions of deaths by 2020 through more equitable access to existing vaccines. The dimensions of equity that will require consideration include disparities between countries, adolescent and adult immunization, and immunization during emergencies. Historically, it took decades before vaccines used in high–income countries became available in low– and middle–income countries, and GVAP should address this inequity. (*WHO*, 1 Mar 2013)



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# Demography

According to a study released in 2012 by the Pew Research Center, the birth rate in the USA is the lowest in nearly a century. This trend is a global phenomenon, with women in most places today having fewer kids, and later in life. In 1970 the average woman on the planet gave birth to 4.7 children in her lifetime. By 2011 that number had dropped to 2.5. Even in the world's most fecund region, sub–Saharan Africa, the fertility rate fell from 6.7 to 4.9 between 1980 and 2010, with births among women under 20 dropping by 20% in the 21st century. The combination of falling birth rates and longer life expectancies also means the world is rapidly getting older. In 1970, the median age was 20; in 1980, it rose to 23; by 2050, it will be 38. Meanwhile, the number of people older than 65 years doubled from 5% to nearly 10% between 1970 and 2011 and is expected to further rise to 20% by 2050. Expenditures on the old will skyrocket, with pension spending in the European Union already reaching about 12.5% of GDP. (*BusinessWeek*, 7 Feb 2013)

Antiretroviral (ARV) drugs for HIV have had a profound effect on life expectancy in Africa, a study in the *Science* magazine showed. Adult life expectancy had fallen to only 49 years in KwaZulu–Natal, South Africa, in the year 2003, and widespread use of antiretroviral drugs was introduced in the fall of 2004. From that point, life expectancy kept increasing and reached 60.5 years by 2011. Adult life expectancy is the mean age to which a 15–year–old could expect to live if subjected to the full pattern of age–specific mortality rates observed in a population for a given period of time. (*BMJ*, 21 Feb 2013)

UNICEF's report "Generation 2025 and beyond: the critical importance of understanding demographic trends for children of the 21st century" highlighted that, by the middle of the 21st century, almost one in every three births will be in sub–Saharan Africa. In comparison, this region had just one in ten births in 1950. The main factors contributing to this scenario will be improved child survival and continuing high fertility rates in sub–Saharan Africa, which contrasts with the falling rates in the rest of the world. In 1990, about half the world's children lived in developing countries while by 2025 nearly two–thirds will live in these countries (*The Lancet*, 2 Mar 2013).

One of the most surprising, and perhaps confounding, facts of charity in America is that the poorest people donate the greatest percentage of their income. In 2011, the Americans whose earnings were in the top 20% of the population contributed 1.3% of their income to charity, while those in the bottom 20% donated 3.2%. This difference is further accentuated by the fact that, unlike middle–class and wealthy donors, most of them cannot take advantage of the charitable tax deduction. Some experts now speculate that the wealthy may simply be less generous, because the personal drive to accumulate wealth is inconsistent with the idea of communal support. Dr Paul Piff, a psychologist at UC Berkeley, conducted research that correlated wealth with an increase in unethical behaviour, saying that "...the rich are more likely to prioritize their own self–interests above the interests of other people." (*The Atlantic*, 20 Mar 2013)

In their annual progress report on the MDGs, the World Bank and the International Monetary Fund (IMF) focused on the positive effects of urbanisation. Urbanisation could be a "force for good", providing better jobs and cheaper services and accelerating progress towards the Millennium Development Goals (MDGs). However, careful planning is essential to prevent the growth of slums, pollution and crime, all of which could prevent reaching the agreed targets. The report stated that urbanisation provides higher incomes than workers would earn on a farm and yields many opportunities to climb the income ladder. (*The Guardian*, 17 Apr 2013)

# Economy

The United Nations' report in December 2012 presented a grim economic forecast, described a cycle of austerity, and exposed persistent unemployment in many countries. The triple threat of the 'fiscal cliff' in the United States, the European debt crisis and the economic hard landing in China spared little optimism at the United Nations headquarters. The report's main author, Mr Robert Vos, who is the Director of the Development Policy and Analysis Division of the United Nations Department of Economic and Social Affairs, feared the exacerbation of this economic climate could cause "a new global recession". If this was indeed the case, then the unemployment lost across the United States and Europe since 2008/2009 would be unlikely to recover until as late as 2017. Although the presented proposals on the best strategies to avoid this outcome will not be easily incorporated into the tight budgets of the

United States and Europe, it has still provided one of the most comprehensive assessments of the world's economic landscape and exposed what United Nations experts view as the most pressing areas of concern. (*New York Times*, 18 Dec 2012)

▸▸ In his debut speech to the UN General Assembly, French President Mr Hollande asked attending world leaders to "globalize solidarity" and implement a Financial Transaction Tax (FTT). In a pioneering move, he announced part of the new French FTT will be allocated to development aid; if other nations choose to follow, this move could offer a solution to plugging holes in foreign aid which has been drying up throughout the current economic crisis. There is already evidence that globalization can give back to the global poor using small levies on transactions: UNITAID. This global health organization raised over US$ 2 billion over the last six years through a small levy on air tickets in nine countries including France, Chile and South Korea. This secure line of funding is then used to negotiate the best prices for tests and treatment for HIV/AIDS, malaria and tuberculosis. France has demonstrated that FTT is feasible. (*The Huffington Post*, 10 Jan 2013)

▸▸ The World Bank has published its latest report showing some optimism for growth in the economy, however sluggish this might be. This is largely down to developing countries, which clearly have an accelerating pace of growth. These countries are also driving global increase in goods and service trade, one of the key successes described in the report. However, the report also describes the need for these countries to modify their policy–making away from short–term fixes to counteract the developed world's economical fluctuation, and to focus instead on addressing their domestic economic issues in order to stimulate long–term growth. The chief economist, Mr Kaushik Basu, stated that these countries should strive to "ensure their fiscal and monetary policies are robust and responsive to domestic conditions". (*New York Times*, 15 Jan 2013)

▸▸ The report, by Oxford University's poverty and human development initiative showed that poverty is shrinking rapidly across the globe. Their study has taken a new approach to measuring deprivation. It predicts that countries among the most impoverished in the world could see acute poverty eradicated within 20 years, if they continue to progress at present rates. It identified "star performer" nations, such as Rwanda, Nepal and Bangladesh, where it predicts that deprivation could disappear within the lifetime of present generations. Following them closely in rapid reduction in poverty levels are Ghana, Tanzania, Cambodia and Bolivia. (*The Guardian*, 17 Mar 2013)

▸▸ The World Bank's president, Mr Jim Yong Kim, claimed that the recent signs of recovery in the global economy meant that there was now an "opportunity to create a world free from the stain of poverty" by 2030, although the optimistic new target has already divided development experts. The president of the World Bank has warned that ending the extreme poverty within a generation would be more difficult than tackling the AIDS pandemic and he urged direct action to help more than a billion people benefit from growth. He added that the goal of reducing the number of people living on less than US$ 1.25 a day from 21% to 3% by 2030 was achievable, although "extraordinarily difficult". (*The Guardian*, 4 Apr 2013)

# ▸ Energy

▸▸ According to this year's "Poor People's Energy Outlook" report, published by the NGO *Practical Action*, energy poverty has left more than 1 billion people in developing countries without access to adequate healthcare. Medical staff is forced to treat emergency patients in the dark, and health centres lack the power to store vaccines or sterilise medical supplies. In India alone, nearly half of all health facilities – serving almost 600 million people – lack electricity, with a further 255 million people being served by health centres without electricity in sub–Saharan Africa, where more than 30% lack power. Even where health centres do have access to power, frequent power shortages significantly hamper the ability to provide quality care. In Kenya, only 25% of facilities have a reliable energy supply, and blackouts happen at least six times a month, for an average of 4.5 hours at a time, affecting services and leading to wasted vaccines, blood and medicines that require constant storage temperatures. (*The Guardian*, 7 Mar 2013)

▸▸ Galvanized by the "Sustainable Energy for All" initiative, led by UN secretary general Ban Ki–moon, energy has shot up the international agenda. The initiative aims to achieve universal access to energy by 2030, along with efficiency gains and increased use of renewable energy. Non–governmental organizations, however, warn that too little attention has been paid to the needs of critical community services, putting progress on development goals, particularly on health and education, at risk. (*The Guardian*, 7 Mar 2013)

▸▸ According to a report by the Pew Charitable Trusts, China overtook the United States as the global leader in clean

energy investment in 2012, while American spending on renewable energy sources dropped nearly 40%. The report concluded that the center of gravity in the clean energy has shifted from the United States and Europe to China. China's leaders are intensely focused on clean energy, with aggressive targets that helped the rapid growth of the country's solar and wind industries. China attracted US$ 65 billion in clean energy investment in 2012, which is 30% of all renewable investment in the G20 economies. China is installing solar energy partly because the western European market for its solar products is drying up. China is also a major manufacturer of wind turbines. (*The Modesto Bee*, 6 Jun 2013)

▸▸ MarketResearchReports.Biz announced its new report on "Thermoelectric Energy Harvesting 2013–2023: Devices, Applications, Opportunities". Thermoelectric generators are devices that convert temperature differences into electrical energy. The underlying principle phenomenon is known as the Seebeck effect: the conversion of a temperature differential into electricity at the junction of two materials. Although thermoelectric phenomena have been used for heating and cooling applications in the past, electricity generation has only seen limited market, but in recent years that interest has increased. (*WatchList News*, 8 Jun 2013)

▸▸ Chilean businesses seeking to curb their carbon emissions should be able to tap into 600 MW of new, green energy projects. This is due to a new, US$ 1.4 billion joint venture between Mainstream Renewable Power and the investor company Actis. The Ireland–based renewable energy developer confirmed plans to bring 450 MW of wind energy projects and 150 MW of solar power capacity into operation, or at least construction, in Chile by early 2016. Under the terms of the deal, Actis will own 60% of the joint venture while Mainstream will own the remaining 40%. Mainstream will develop all the projects and manage them once they are completed, with the joint venture company investing at the point of financial close for each scheme. In a statement, Mr Eddie O'Connor, Mainstream's chief executive, said the new projects were "...primarily aimed at helping to curb emissions from large industrial businesses in the country". (*Business Week*, 10 Jun 2013)

# Environment

▸▸ The year 2012 was among the 10 warmest years on record, as reported by agencies such as National Oceanic and Atmospheric Administration (NOAA) and NASA. The global temperatures in 2012 were higher than the long–term average for the 36$^{th}$ consecutive year. It appears that the average global temperature has risen about 1.4F since the year 1880. NASA declared the year 2012 as the 9$^{th}$ hottest year on record, while NOAA ranked it 10$^{th}$ on record. (*The Guardian*, 16 Jan 2013)

▸▸ In his inaugural address, the US President Mr Barack Obama made climate change a second–term priority. It is now emerging that he could bypass Congress to implement much of his environmental agenda unilaterally. He could revive the failed 2009 cap–and–trade legislation through regulation, with legal authority derived from the four–decade–old Clean Air Act, and a 2007 Supreme Court decision applying it to carbon emissions. This should allow imposing curbs on coal–fired electric plants and limit methane emissions from hydraulic fracturing, according to environmentalists' sources. (*Bloomberg*, 23 Jan 2013)

▸▸ A poll was conducted among 200 000 people to propose six life–changing priorities for their local environments to help planning post–2015 global agenda. One of the top three priorities in the world as a whole, for both men and women, for people of all ages, and in all types of countries was "an honest and responsive government". The other two priorities consistently in the top three for most groups were a good education and better healthcare. (*The Guardian*, 25 Mar 2013)

▸▸ The Hunger–Nutrition–Climate Justice (HNCJ) conference, held in Dublin, Ireland, considered the issue of joint effects of climate change and hunger on the poor nations from the perspective of "climate justice". This is an approach to climate change focusing on the rights of vulnerable people who are the least responsible for causing climate change, but among the most affected. (*IRIN,* 24 Apr 2013)

▸▸ Most of the attention on global environmental issues goes to climate change, and the carbon dioxide we're adding to the atmosphere may already be changing the climate for the worse. However, according to researchers from New York's Mount Sinai Medical School and the Blacksmith Institute, a NGO that focuses on industrial pollution in the developing world, high lead exposure in small children may be an even more pressing immediate issue. It has been linked to many complications later in life, including lower IQ, hyperactivity, behavioural problems and learning disabilities. This is a disorder of the

poor, who live in the crowded urban tenements and near toxic industrial sites. In the postwar era, lead contamination was common even in wealthy countries because of the widespread use of leaded gasoline, paints and soil; when it was removed in the 1970s, lead contamination plummeted, with blood lead levels among pre–school children reducing from 16.5 micrograms/dl in 1978 to just 3.6 in 1993. Getting lead out of the environment might have been one of the most important public–health actions the US has ever taken. (*TIME*, 8 May 2013)

# Food, Water and Sanitation

The UK Institute of Mechanical Engineering's (IMechE) report on food waste estimated that 30–50% of food produced globally is wasted. In less developed countries this waste is largely due to poor practices in harvesting, storage and transportation. In developed countries the wastage mainly occurs further along the line of food production and consumption, due to behaviour of supermarkets and consumers. In the UK, for example, up to 30% of the vegetable crop is rejected because it does not conform to the narrow range of physical characteristics required by the major supermarkets, with further 30–50% of food discarded by the purchaser. The report stated that eliminating the waste could provide 60–100% more food for consumption. To help prevent a global food crisis, the IMechE report recommended that engineers should be involved in improving food production in developing countries, while rapidly developing countries should incorporate 'waste minimisation thinking' into their planning of transport and storage facilities, and high–income countries should work on changing consumer behaviour. (*The Guardian*, 07 Jan 2013)

More than 150 organisations and charities have banded together to create the "*enough food for everyone IF*" campaign, which aims to lobby MPs and bring hunger to the world agenda at the G8 summit. The campaign is based on the principle that the world can produce enough food to sustain its population if the richest nations tackle the "four big IFs": (i) provide enough aid to help families feed themselves and prevent children dying from hunger; (ii) stop big companies from tax–dodging in developing countries; (iii) prevent poor farmers from being forced out of their land, and allow them to grow food, not fuel; and (iv) governments and big companies become transparent about their actions which act as barriers to people getting enough food. This is the largest collaboration in the charity sector since the 2005 "*Make Poverty History*" campaign. It focuses on the responsibility and accountability of governments and international corporations. Critics have reflected that the campaign is too similar to the "*Make Poverty History*" campaign and risks losing public interest by the apparent lack of change since 2005. (*BBC News*, 23 Jan 2013)

At the current rate of progress, the world is set to miss the global sanitation target for 2015 by over half a billion people. More people today have access to a cell phone than to a clean toilet. While the drinking water global target was met last year, nearly a billion people still lack access to an improved drinking water source. The World Bank estimated that economic cost of the water and sanitation crisis result in economic losses estimated at US$ 260 billion annually in low– and middle–income countries, which is about 1.5% of their cumulative GDP. (*The World Bank / The Water Blog*, 11 Feb 2013)

The Hunger–Nutrition–Climate Justice (HNCJ) conference, held in Dublin, Ireland, was organized by Irish Aid, the Mary Robinson Foundation, CGIAR and the World Food Programme (WFP). Studies conducted in Ethiopia, India, Kenya and Niger showed that children born during natural hazards, like droughts or floods, are more likely to be malnourished, while poor countries, which are already struggling with hunger and food insecurity, are increasingly likely to face these natural hazards. "Joined–up approach" – also known as the "nexus" approach – seeks to find solutions for such circular problems based on the interconnections between various sectors or disciplines. For instance, addressing interconnected malnutrition and climate change problems would involve working across health, agriculture, environment, water and land management sectors. (*IRIN*, 24 Apr 2013)

Researchers from the Potsdam Institute for Climate Impact Research, Germany, calculated the food growing capacity of every country in the world and compared it with food requirements in the present, and projected forward to 2050. Their model employed climate data, soil type and land–use patterns, population projections and food and water consumption. Although many countries choose to import food right now, the model showed that there are surprisingly few – 66 countries, or 16% of the world's population – that could not maintain the same diet and still be food self–sufficient. The countries with the most reliance on imports were found in North Africa, the Middle East and Central America. However, over half of the world's population could depend on imported food by 2050. Potsdam Institute projection suggests population growth would increase imported food, even without climate change, because they are limited by lack of land or water. (*The Guardian*, 7 May 2013)

# Peace and Human Rights

According to a large international study of national defence ministries and armed forces, most countries lack the tools to prevent corruption in the arms trade. Transparency International's (TI) report showed that a number of most lucrative potential markets for arms, including Saudi Arabia, Indonesia and Oman, are also among countries with "a very high risk" of corruption. TI's Government Defence Anti–Corruption Index analyses measures by 82 countries to reduce corruption risks. (*The Guardian*, 29 Jan 2013)

A new UN report estimated that millions of people are still being trafficked for sexual exploitation and forced labour. The encountered victims were from at least 136 different nationalities, and they have been detected in 118 countries. The majority of victims are women, although the number of children is also increasing. (*Miami Herald*, 12 Feb 2013)

United Nations officials joined millions of people globally who took a stance against violence against women. This public action was a part of the "One Billion Rising" campaign – sponsored by the V–day Organization – which seeks to mobilize men and women around the world on Valentine's Day. The aim of the campaign is to stop violence against women and girls, including rape, battery, incest, female genital mutilation (FGM), and sex slavery. (*UN News*, 14 Feb 2013)

In an excellent analysis, Ms Mary Robinson, Mr Kevin Rudd and Ms Judy Cheng–Hopkins suggest that peace, security, good governance and the rule of law must be included in the new Millennium Development Goals. They remind that, in September 2000, world leaders unanimously adopted the Millennium Development Goals (MDGs) – a series of specific targets for poverty eradication, universal primary school enrolment, gender equality, reduction in child and maternal mortality, combating major disease and ensuring environmental sustainability. The MDGs encouraged developing countries and the rest of international community to take concrete and tangible steps towards achieving the set targets, with a notable progress along the way. However, a sobering fact is that no fragile or conflict–affected low–income country has managed to achieve a single MDG. (*The Huffington Post*, 12 Mar 2013)

The newly elected Pope Francis declared that he "... would like to see a church that is poor and is for the poor". The first Latin American and the first Jesuit pontiff explained to the media that he chose to name himself after St Francis of Assisi, because the saint devoted his life to peace and the poor. In a clear signal of his desire to reset the priorities of the embattled Catholic Church after Benedict XVI's intellectual, remote–seeming reign, Francis added that the reminder had made him think of St Francis – a man "who wanted a poor church". Only 16% of the world's population is presently Catholic, but some 42% are Latin American and 15% African. (*The Guardian*, 16 Mar 2013)

# Science and Technology

Mobile phone technology is frequently proposed as an attractive solution to address health challenges in low resource settings. However, two recent reviews – on the impact of mHealth on behaviour change and service delivery – didn't manage to find proper evidence that mHealth really works in a desired way. Only three of 75 trials that assessed mHealth's impact on health behaviour change or improved disease management were conducted in low– or middle–income countries. Further high quality trials are required to establish the true potential and effectiveness. (*SciDev.Net*, 15 Jan 2013)

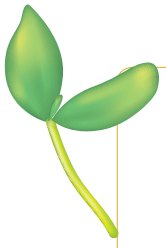
The first major trial of a new booster vaccine against tuberculosis (TB) since Bacillus Calmette–Guerin (BCG) was introduced in 1921 has failed. BCG is only partially effective against the mycobacterium that causes TB and there are several ongoing efforts to introduce new vaccines. The latest, MVA85A, failed to protect babies who already received BCG. The trial was conducted in South Africa and involved 2794 healthy children aged four to six months, half of whom were vaccinated and then followed up for an average of two years. The researchers found 32 cases of TB in those who had received the vaccine and 39 in the placebo group, i.e. not a significant result. (*BBC*, 4 Feb 2013)

The intrinsic value of the "Human Genome Project", completed in 2003 with mainly public resources, has since been circumscribed by the expansion of intellectual property rights over genomic DNA. An estimated 20% of the human genome is now subject to patents that can impose complex legal and cost constraints on medicines and diagnostics. The key issue is not an argument against patenting

of inventions based on "modified" gene sequences, but rather the practice that enables the isolated, but otherwise unmodified, genomic DNA to be included in patent claims. This intellectual property practice is not universal, and countries such as Brazil do not allow this practice, but its intellectual property framework is nevertheless consistent with World Trade Organization intellectual property obligations. In January, the European Parliament questioned whether those responsible for important policy matters understood the consequences for the developing world of allowing intellectual property rights over unique products of nature, such as the human genome. The 2002 "Genomics and World Health" report of the World Health Organization's advisory committee on health research highlighted problems with patents locking away the use an original gene sequence, with the follow–up initiative in 2010 suggesting options to deal with a growing "genome divide". However, until recently little scrutiny has been applied to legal and policy frameworks that enable the incremental expansion of intellectual property rights into this scientifically important area of health. (*The Guardian*, 12 Mar 2013)

▸▸ The Canada Gairdner International Awards honoured three areas of research in 2013: Drs Harvey J. Alter and Daniel W. Bradley received the award for their contributions to the discovery and isolation of the hepatitis C virus, with Dr Michael Houghton also selected, but declining to receive the award. Dr Stephen Joseph Elledge was recognized for his work in DNA repair, while Sir Gregory Winter was honoured for creating synthetic human antibodies. Dr King K. Holmes was selected for the Canada Gairdner Global Health Award for his work on defining and treating HIV and other sexually transmitted diseases, and The Canada Gairdner Wightman Award went to Dr James C. Hogg for his research and leadership in the field of chronic respiratory diseases. (*Gairdner Foundation*, 20 Mar 2013)

▸▸ Scientists studying tuberculosis (TB) patients in Tamil Nadu, India, have found that a quarter were diabetes sufferers. The connection between the two diseases that has already been recognised in industrialised countries, and is emerging even more strongly in regions such as Asia and Africa. According to Dr Anil Kapur, managing director of the World Diabetes Foundation, which funded the project, "...people with diabetes in the developing world are two or three times more likely to contract TB, compared with those without diabetes". Moreover, having diabetes seems to reduce response to TB treatment, so that one disease reinforces the adverse effects of the other. (*Financial Times*, 21 Mar 2013)



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# Global visibility for global health: Is it time for a new descriptor in Medical Subject Heading (MeSH) of MEDLINE/PubMed?

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Despite a large body of research in global health (almost 9000 articles published in PubMed until 2012), the term "global health" is not included in the Medical Subject Headings (MeSH) of the NLM – its controlled vocabulary thesaurus which NLM uses to index articles in MEDLINE. There are only 6 journals currently covered by PubMed which specialize in global health, including *Journal of Global Health*.

A PubMed search using the term "global health" [All Fields] retrieves 8975 articles published up to the end of 2012. This is a large body of evidence for a new discipline in health research, defined in 2009 as 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" [1].

## PUBMED HISTORY OF GLOBAL HEALTH

According to PubMed, the first article that mentions global health was published already in 1966, describing "global health factors of importance" to military forces with worldwide engagement [2]. The term "global health" was again used 10 years later, in 1976, in an article that recognized blindness and its prevention as a global health problem; the article was published in a Swedish general medical journal [3]. From 1979, there is a steady flow of articles related to global health, with a major increase from 2006 onwards (**Figure 1**), paralleled by a dramatic increase in academic involvement in global health training programmes [4]. In 2010 and 2011, the number of articles containing the term "global health" went over a thousand, and then almost doubled in 2012, the year which closed with 2136 articles (**Figure 1**). At the time of finishing this viewpoint (search performed on 29 May 2013), the number of articles in less than the first 5 months of 2013 was 1165, indicating a continuing rapid growth of global health research.

## GLOBAL HEALTH AS A BIBLIOGRAPHICAL CONCEPT

Despite such volume of research output in global health, the term "global health" is not included in the Medical Subject Headings (MeSH) of the NLM – its controlled vocabulary thesaurus which NLM uses to index articles in MEDLINE [5]. NLM states that its indexers include new terms in MeSH "as they appear in the scientific literature or in emerging areas of research". Search of MeSH for the truncated term "global" returns 52 terms, mostly related to pro-

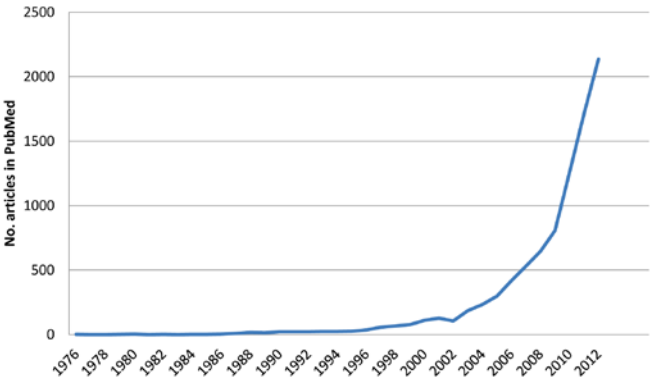


**Figure 1.** Number of articles indexed in PubMed which contained "global health" as a term anywhere in the text or bibliographical information.

tein biochemistry. Only 7 terms have some relevance to global health, such as "Global Warming" (introduced in 2010), "Disease Eradication" (introduced in 2012), "Carbon Footprint" (introduced in 2011), "World War I" and "World War II" (introduced in 2005), "Greenhouse Effect" (introduced in 1994) and "Transcultural Nursing" (introduced in 1992). It is interesting that "Global Warming" is a MeSH term although the number of articles using this term is almost 3 times smaller than that for "global health". PubMed search for "global warming" ("global warming"[All Fields]) retrieves 3054 articles until the end of 2012, with the highest annual output of 504 articles in 2012.

The only term related to global health in MeSH is "World Health", introduced in 1978 and defined as "The concept pertaining to the health status of inhabitants of the world". This term does not adequately cover the current concept of global health [1], just as the term "burden of disease" is not adequately covered by the concept "Cost of Illness" ("The personal cost of acute or chronic disease") where it maps in a MeSH search.

## JOURNALS SPECIALIZED IN GLOBAL HEALTH

In addition to the lack of conceptualization of global health in the largest collection of medical literature, there are only 4 journals currently indexed in MEDLINE that have global health in their focus, according to the search of the Catalog of the National Library of Medicine (NLM) using the search strategy: "global health"[All Fields] AND (ncbijournals [All Fields] AND currentlyindexed[All]). These journals are *Pathogens and Global Health*, *Global Health Promotion*, *Global Health Action*, and *Globalization and Health*. The search of the NLM Catalogue for the journals indexed in PubMed Central and thus also available in PubMed [6] identifies 2 more journals: *Emerging Microbes & Infections* and *Journal of Global Health*.

> I propose the inclusion of "global health" as a MeSH term in order to recognize the new research discipline in health. This will greatly assist in finding relevant evidence about global health issues and facilitate the translation of knowledge to practice at all levels of health care.

## *JOURNAL OF GLOBAL HEALTH (JoGH)* – PRESENT AND FUTURE

Yes, one of 6 journals in PubMed dedicated to global health is *Journal of Global Health* (*JoGH*), the journal we started 2 years ago for reason described above – the need to communicate rapidly accumulating research on health issues with global impact [7]. Two years later, the data on journal visibility fully justify its launch. Particularly important was the inclusion of the journal in PubMed Central, NLM's digital journal repository [6], which also made all journal issues available in PubMed. PubMed coverage increased access to articles both via PubMedCentral and the journal site.

According to Google Analytics© breakdown of *JoGH* web–site traffic 12 months before (1 December 2011 to 30 November 2012) and 6 months after PubMed coverage (1 December 2012 to 31 May 2013), direct visits to journal's website (http://jogh.org) increased from about 10 to 17 visitors per day, with a substantial growth in the category of "new visitors" (58.7% vs 71.2% before and after PubMed coverage, respectively). Daily maximum increased from 35 to 48 visits, and daily minimum from 1 to 4 visits. PubMed

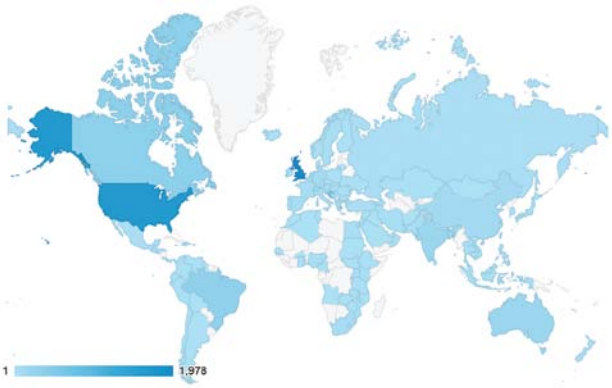


**Figure 2.** Journal's global impact: in the 18 months between December 2011 and May 2012, the website of *Journal of Global Health* was visited 6805 times, attracting visitors from 1233 cities in 128 countries (Source: Google Analytics©). The largest number of visits (n = 1978) was from United Kingdom, closely followed by the USA (n = 1669).

coverage also facilitated a truly global access to the journal's website. In total (18 months between Dec 2011 and May 2012, the website has been visited 6805 times, attracting visitors from 1233 cities in 128 countries (Source: Google Analytics©). The largest number of visits (n = 1978) was from United Kingdom, closely followed by the USA (n = 1669) (**Figure 2**).

The usage through PubMed directly is even more impressive (**Figure 3**). In the month when *JoGH* became available in PubMed Central (December 2012), the total number of visits to the journal's content increased 10–fold, to more than 3500 visits per month in the first 3 months. The visits came from all over the world, and PubMed coverage increased those from developing countries. A total of 18 194 requests for full–text articles were recorded through PubMed Central within the first six months (December 2012 – May 2013).

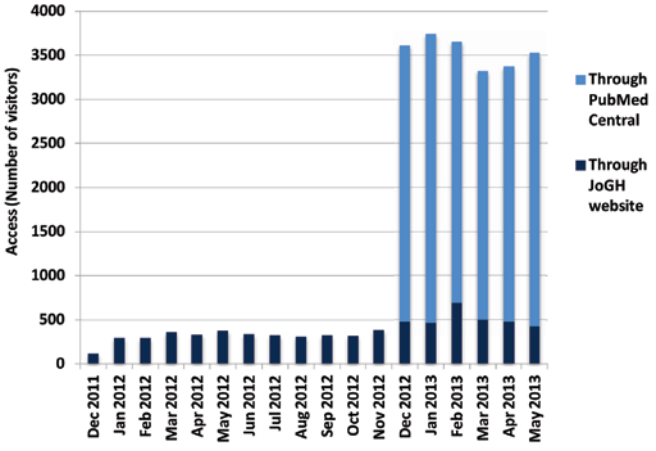


**Figure 3.** Access to the content of *Journal of Global Health* (*JoGH*), measured in number of visitors to the website (http://jogh.org) and number of visitors to journal's PubMed Central site (December 2011 – May 2013).

**Photo: Courtesy of David Hipgrave, personal collection**

The top 10 most accessed and downloaded articles during the first six months (December 2012 – May2013) of *JoGH*'s availability via PubMed are shown in **Table 1**. The authors of these papers come from different countries, both high–income and low– and middle–income countries, and different world regions.

The interest of *JoGH* readers is clear – they want high–quality systematic reviews and viewpoints on those issues that

**Table 1.** Top 10 most accessed articles in *Journal of Global Health* via PubMed Central, December 2012 – May 2013

| Rank | Author | Title | Full text | PDF download | Total requests |
|---|---|---|---|---|---|
| 1 | Meem M et al. | Biomarkers for diagnosis of neonatal infections: A systematic analysis of their potential as a point–of–care diagnostics | 1068 | 677 | 1745 |
| 2 | Jawad I et al. | Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality | 749 | 352 | 1101 |
| 3 | Buckle GC et al. | Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010 | 807 | 283 | 1090 |
| 4 | Roberts T et al. | Epidemiology and aetiology of maternal parasitic infections in low– and middle–income countries | 635 | 364 | 999 |
| 5 | Bahl R et al. | Setting research priorities to reduce global mortality from preterm birth and low birth weight by 2015 | 619 | 315 | 934 |
| 6 | Waters D et al. | Aetiology of community–acquired neonatal sepsis in low and middle income countries | 607 | 231 | 838 |
| 7 | PalaniVelu P et al. | Epidemiology and aetiology of maternal bacterial and viral infections in low– and middle–income countries | 589 | 174 | 763 |
| 8 | Torti J | Floods in Southeast Asia: A health priority | 654 | 61 | 715 |
| 9 | Hipgrave D | Communicable disease control in China: From Mao to now | 526 | 146 | 672 |
| 10 | Kolčić I | Double burden of malnutrition: A silent driver of double burden of disease in low– and middle–income countries | 429 | 111 | 540 |

are relevant for the global community, followed by regional issues with a global relevance and impact (**Table 1**). In future, *JoGH* will continue its mission of publishing high–quality peer–reviewed original research, objective reviews and personal viewpoints of global health and development issues [7]. As a member of the Committee of Publication Ethics (COPE), *JoGH* will keep follow the best practices in scientific publishing and ensure the integrity of the published record [8].

## PROPOSAL TO MEDLINE/PubMed

The analysis of records in different databases of the largest global medical library, NLM, clearly demonstrated how a phenomenal increase in global health research has not been followed by systematic conceptualization in recording the publication output from this research, as well as capturing sources of global health research information. I propose the inclusion of "global health" as a MeSH term – to recognize the new research discipline in health. This will greatly assist in finding relevant evidence about global health issues and facilitate the translation of knowledge to practice at all levels of health care.

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# Setting priorities for development of emerging interventions against childhood diarrhoea

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An expert panel exercise was conducted to assess feasibility and potential effectiveness of 10 emerging health interventions against childhood diarrhoea. Twelve international experts were invited to take part in a CHNRI priority setting process. This group used 12 different criteria relevant to successful development and implementation of the emerging interventions, nine of which were retained in the final analysis. They showed most collective optimism towards developing household or community-level water treatment, followed by sustainable, affordable latrine options; those two emerging interventions were followed by antibiotic therapy of *Cryptosporidium diarrhoea*, and oral or transcutaneous enteric vaccine development.

Diarrhoeal diseases are still among the leading causes of childhood mortality in the world, contributing to more than 800 000 deaths in children younger than 5 years of age in 2010 [1,2]. It is widely acknowledged that a major portion of those deaths can be prevented if universal coverage of known effective interventions could be achieved [3,4]. However, recent evaluations have shown that the uptake of those interventions is rather disappointing, with only a minority of all children with life–threatening episodes of diarrhoea in low– and middle–income countries having access to trained health care providers and receiving appropriate treatment [5–7]. Thus, novel diarrhoea control strategies that balance investments in scaling up of existing interventions and the development of novel approaches, technologies and ideas are needed.

The importance of childhood diarrhoea as a global public health problem is in stark contrast to the size of the research community focused on the issue and the amount of funding committed to studying the disease [8]. However, there have been several efforts in recent years that aimed

to mobilize the research community and encourage research on childhood diarrhoea. Kosek et al. used the Child Health and Nutrition Research Initiative (CHNRI) methodology to define research priorities that could immediately reduce the burden of disease [9]. This was followed by the World Health Organization's CHNRI exercise that defined research priorities to reduce global mortality from childhood diarrhoea by the year 2015, ie, the time of the fourth Millennium Development Goal's target [10]. Recently, a new initiative has been launched – Global Action Plan for Pneumonia and Diarrhoea (GAPPD) – which prioritizes a research agenda for childhood diarrhoea beyond 2015 [2–4,11]. The results of their very comprehensive CHNRI process, with the timeline extended 15 years ahead and an expanded scope of research on preventing morbidity, have been published recently[12]. The purpose of this exercise was to further contribute to the active field of setting research priorities for childhood diarrhoea, by reviewing the landscape of new ideas and/or novel potential interventions – hereby referred to as "emerging interventions" – and set priorities for investments in their development.

The second level of priority was assigned to probiotics and prebiotics; combination vaccine for *Cryptosporidium, Shigella* and enterotoxigenic *Escherichia coli* (ETEC); and to the use of anti-emetics in case management. The lowest level of enthusiasm was expressed towards the treatment or prevention (vaccines) of environmental enteropathy, CFTR inhibitors, and the inhibitors of intestinal epithelial secretion in the treatment of diarrhoea. The exercise suggested that there are relatively few novel or feasible interventions in the course of development to address the high residual disease burden of diarrhoea in children.

## EMERGING INTERVENTIONS AGAINST CHILDHOOD DIARRHOEA

The 10 emerging interventions were chosen for evaluation from the results of a previous CHNRI exercise [12] and further consultation with a paediatric gastroenterologist (**Table 1**).The previous exercise [12] brought together 10 teams, corresponding to research avenues in childhood diarrhoeal disease. Each team separately generated and ranked their set of research questions. While one team focused specifically on emerging interventions, many teams generated research priorities related to emerging interventions and thus, we considered novel interventions proposed by all teams for inclusion in this exercise. We aimed to be open–minded and inclusive in the selection of these interventions, appreciating that some of them may still need considerable work before being ready for implementation.

## EXPERT OPINION EXERCISE

The CHNRI methodology for priority setting in investments in health research and technologies was proposed as a systematic tool that can be used to develop research policy and/or prioritize investments in health research [13–14]. The CHNRI method consists of the following steps: (i) investors and policy–makers define the context of the problem and identify the criteria for priority–setting; (ii) technical experts generate research priorities and score them against the pre–defined criteria; and, (iii) other stakeholders decide on the weight of the criteria, intended to reflect a wider societal system of values. The method has been described elsewhere, and many examples of implementation have been published [15–18].

A group of 12 leading international experts were invited to participate in the expert opinion exercise. The group was instructed to use a downstream (ie, broad, long–term) approach and focus solely on emerging interventions. During October 2012 the group ranked 10 emerging interventions according to a number of criteria used to identify priorities for research support in the area of childhood diarrhoea. A

**Table 1.** The consolidated list of 10 emerging interventions against childhood diarrhoea

| |
|---|
| 1. Probiotics and prebiotics |
| 2. Anti–emetics |
| 3. Treatment or prevention (vaccines) of environmental enteropathy |
| 4. Sustainable, affordable latrine options |
| 5. Household– or community–level water treatment |
| 6. CFTR inhibitors |
| 7. Inhibitors of intestinal epithelial function in the treatment of diarrhoea |
| 8. Antibiotic therapy of *Cryptosporidium* diarrhoea |
| 9. Oral or transcutaneous vaccine development |
| 10. Combination vaccine for *Cryptosporidium*, *Shigella*, and enterotoxigenic *Escherichia coli* (ETEC) |

CFTR – cystic fibrosis transmembrane conductance regulator

modified version of CHNRI's conceptual framework (**Table 2**) was used and included 12 criteria for prioritization of emerging interventions: 1) answerability (in an ethical way); 2) low development cost; 3) low product cost; 4) low implementation cost; 5) predicted efficacy; 6) likelihood of deliverability; 7) likelihood of affordability; 8) likelihood of sustainability; 9) maximum potential impact on mortality burden reduction; 10) likelihood of acceptability to health workers; 11) likelihood of acceptability to end users; 12) predicted impact on equity [19].

All experts invited to participate in the exercise received a brief (1 page) background document containing information on each of the 10 emerging interventions. This document also explained why each of the 12 criteria was chosen and how to apply them to each emerging intervention. The experts were free to challenge all information provided to them in a background document and to share further personal knowledge or opinion with the group. The experts were invited by e–mail to score, independently of each other, all emerging interventions according to the 12 agreed CHNRI criteria.

The scoring of the emerging interventions was conducted using a points system that assigned a value of 1 to positive answers (yes) and 0 to negative answers (no). When an expert assigned the answer "undecided" to a given criteria, the value of 0.5 points was used. Conversely, when the expert declared to be insufficiently informed on a given issue to answer the question, the input was deemed missing and not scored (or penalized). Each research question/theme received a score for all 12 criteria from each expert and the final score was calculated as the average of the ratios of the sum of all points given over the maximum possible number of points (excluding missing inputs). Such final score ranged from 0 to 100% and represents a direct measure of 'collective optimism' for a given emerging intervention.

In the initial exercise, we included different components of the cost (development cost, product cost, implementation cost and affordability), but those 4 criteria are in fact a single criterion (cost). We therefore decided to exclude 3 criteria to ensure the remaining criteria were relatively independent of one another (similar to principal component analysis). If all 4 were kept in the exercise, this would give

**Table 2.** Specific questions used to assess whether the proposed research themes (eg, emerging interventions) satisfy the 12 priority–setting criteria

| |
|---|
| **1. Answerability in an ethical way** *("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 2025? |
| • Do we have a sufficient level of funding support to make the intervention available on the market by 2025? |
| • Would you say that it is likely that the remaining technical hurdles can be overcome to make the intervention available on the market by 2025? |
| **2. Low development cost***("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 |
| **3. Low product cost***("1" for Yes;"0" for N;"0.5" for Undecided)* |
| • Is it likely to be a low–cost intervention (ie, <US$ 3.50 per unit?) |
| **4. Low implementation cost***("1" for Yes; "0" for N; "0.5" for Undecided)* |
| • Can we use the existing delivery mechanisms without major modifications (eg, training, infrastructure)? |
| **5. Affordability***("1" for Yes; "0" for N; "0.5" for Undecided)* |
| • Is achievement of a near–universal coverage likely to be affordable to most developing countries? |
| **6. Predicted efficacy** *(0–100%)* |
| • Please assess the likelihood (0–100%) that adequately powered randomized controlled trials of the interventions conducted in developing countries would consistently show statistically significant reduction in cause–specific mortality from childhood diarrhoea. |
| **7. Likely maximum potential impact on mortality burden** |
| • Please predict the proportion of deaths in children under 5 years of age due to diarrhoea that could be averted if the complete coverage with the emerging interventions listed below could be achieved? |
| **8–9. 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. Sustainable for at least 10 years after the time of introduction? |
| **10–12. Acceptability to health workers; Acceptability to end–users; and Impact on equity** *("1" for Yes;"0" for N;"0.5" for Undecided)* |
| • Taking into account the overall context, intervention complexity, health workers' behaviour 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 years following the introduction? |


**Photo: Courtesy of Alice Graham, personal collection**

an undue four–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. After the exclusion, mean scores given to each criterion by the experts was calculated. The overall research priority score (RPS) was calculated as a mean of the 9 intermediate criteria scores. The scores given to all 10 emerging interventions are presented in **Table 3**.

## MAIN FINDINGS

As shown in **Table 3**, the panel declared most of their collective optimism towards developing household– or community–level water treatment, followed by sustainable, affordable latrine options. The key strengths of those interventions were high likelihood of efficacy, acceptability both among health workers and end–users, and positive impact on equity in the population. Those two interventions were followed by antibiotic therapy for *Cryptosporidium* diarrhoea, and oral or transcutaneous enteric vaccine development. These two emerging interventions had similar scores as the two top–ranked, but their impact on equity in the population was deemed less certain.

The second priority level was assigned to probiotics and prebiotics; combination vaccine for *Cryptosporidium*, *Shigella*, and enterotoxigenic *Escherichia coli* (ETEC); and the use of anti–emetics in diarrhoea case management. The key weaknesses of the combination vaccine were uncertain answerability and high predicted cost of development, while the key uncertainty over the use of probiotics and anti–emetics is related to very low optimism towards their potential for the reduction of the overall burden of diarrhoea.

The lowest level of optimism was expressed towards the treatment or prevention of environmental enteropathy, cystic

**Table 3.** The results of the CHNRI exercise: 10 emerging interventions with 9 intermediate scores and an overall research priority score (RPS)

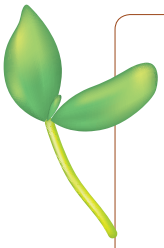
| Rank | Emerging intervention | Answerability | Low development cost | Likelihood of efficacy | Max burden reduction potential | Deliverable | Sustainable | Acceptable to health workers | Acceptable to end users | Impact on equity | Research investment priority score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Household– or community–level water treatment | 78 | 47 | 100 | 44 | 68 | 77 | 95 | 86 | 100 | 77.3 |
| 2 | Sustainable, affordable latrine options | 64 | 60 | 95 | 45 | 41 | 86 | 91 | 95 | 91 | 74.4 |
| 3 | Antibiotic therapy of *Cryptosporidium* diarrhoea | 72 | 49 | 82 | 23 | 64 | 77 | 86 | 91 | 70 | 68.2 |
| 4 | Oral or transcutaneous vaccine development | 44 | 36 | 77 | 39 | 64 | 64 | 100 | 95 | 82 | 66.9 |
| 5 | Probiotics and prebiotics | 74 | 54 | 60 | 10 | 59 | 86 | 77 | 86 | 64 | 63.5 |
| 6 | *Cryptosporidium*, *Shigella*, and enterotoxigenic *Escherichia coli* (ETEC) | 42 | 29 | 82 | 33 | 55 | 68 | 100 | 86 | 73 | 63.1 |
| 7 | Anti–emetics | 65 | 50 | 59 | 7 | 64 | 67 | 91 | 95 | 45 | 60.4 |
| 8 | Treatment or prevention (vaccines) of environmental enteropathy | 29 | 53 | 41 | 39 | 45 | 41 | 80 | 60 | 60 | 49.9 |
| 9 | CFTR inhibitors | 35 | 42 | 55 | 9 | 15 | 30 | 61 | 61 | 28 | 37.4 |
| 10 | Inhibitors of intestinal epithelial function in the treatment of diarrhoea | 38 | 36 | 45 | 21 | 36 | 36 | 44 | 56 | 39 | 39.1 |

CFTR – cystic fibrosis transmembrane conductance regulator

fibrosis transmembrane conductance regulator (CFTR) inhibitors, and the use of inhibitors of intestinal epithelial function in the treatment of diarrhoea. These three interventions had uncertain answerability and effectiveness, with low scores on deliverability, sustainability and acceptability. These interventions were also deemed to have negative impact on equity following their implementation (**Table 3**).

## CONCLUSION

In contrast to very large significance that childhood diarrhoea still has as a public health problem in low and middle income countries, this exercise suggested that relatively few novel interventions can be considered feasible at this point. The experts were most optimistic about the potential for Water and Sanitation Hygiene (WASH) interventions to be efficacious and reduce inequities. Although there are high development costs associated with most of the emerging interventions, investments in this sector will help reduce inequities and reduce the burden of childhood diarrhoea. In synergy with powerful interventions that are currently available, diarrhoeal mortality could be significantly reduced in the next 15 years.



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# The reform of the essential medicines system in China:

# A comprehensive approach to universal coverage

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To achieve universal health care coverage, the Government of China invested in large–scale health care reform. One of the major reform components focuses on improving access to essential medicines to reduce high out–of–pocket medicines spending. The reform policies were comprehensive, and included systematic selection of essential medicines to improve availability, centralized procurement and tendering at provincial levels, pricing policies, provision of essential medicines at cost in primary level facilities, and stronger quality and safety standards. While challenges remain, China's system sets an example of a comprehensive approach that other countries could emulate in reforming their health care systems and achieving universal coverage.

In OECD countries, medicines spending accounts for approximately 17% of total health spending or 1.5% of gross domestic product (GDP) [1]. New technologies and pharmaceuticals have been important contributors to rising health care costs. At the same time, patients may not have access to cost–effective medicines because of lack of health insurance coverage, limited insurance benefits, high medicines prices, physician prescribing choices, or differences between available essential medicines and consumer demand [2]. With the exception of a few countries [3], however, the approach to reform tends to be piecemeal rather than comprehensive.

With the goal of universal health care coverage by 2020, the Government of China has implemented comprehensive health care reforms nationwide [4]. Between 2009 and 2011, the reforms focused on increasing access to essential medicines as well as expanding health insurance, strengthening the primary care system, financing public health, and reforming public hospitals [5]. By 2011, government investments in health reform reached Yuan 1.13 trillion (US$ 174 billion, at Yuan 6.5 per US$) [6]. Total health expenditures increased from 3.5% to 5.0% of GDP between 1995 and 2010 – amounting to an increase from US$ 21 to US$ 220 per capita [7].

The reform of the essential medicines system is a major focus of the national reform agenda. Spending on medicines accounted for 41.9% of total health expenditures in 2010, or 2.1% of GDP (**Figure 1**) [7]. In this paper, we review existing literature, published government documents about the essential medicines reform in China, and literature on essential medicines and health care reform internationally. The paper first presents economic and demographic trends to explain rapid increases in medicines consumption across

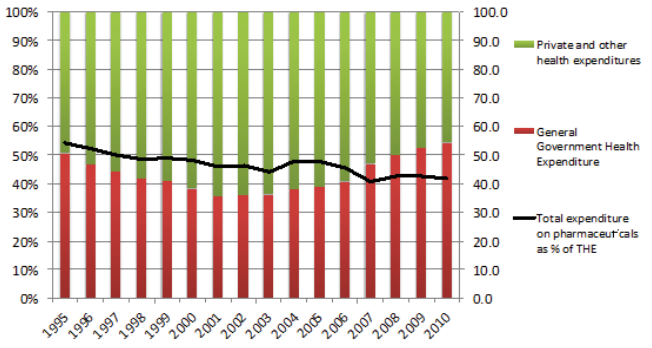



**Figure 1** Private and general government health expenditures, and percent of total health spending devoted to pharmaceuticals, 1995–2010. Source: ref. [7].

China. The 2009 health care reform is discussed, in terms of each component's linkage with medicines reforms. We discuss in detail the reform of the essential medicines system, including the Essential Medicines List (EML), procurement, pricing, financing, and quality. We conclude that China's comprehensive approach in reforming its essential medicines system could be a model for other countries that strive to ensure access to medicines while also controlling costs.

## ECONOMIC AND DEMOGRAPHIC TRENDS DRIVING ESSENTIAL MEDICINES CONSUMPTION

Economic and demographic factors have resulted in increased demand for essential medicines. GDP growth is projected at 7.5% in 2012 [8]. Positive economic growth increases the government's ability to invest in reforms, and household disposable income has also increased between 2008 and 2011 [9]. Strong correlations exist between provincial wealth and spending on medicines, as illustrated by the average medicine spending per inpatient visit by province (**Figure 2**).

Urban residents tend to have higher disposable income, and access to a greater supply of medical products and services. In 2011, average inpatient fees in urban areas were US$ 1340 – nearly twice as high compared with rural areas (US$ 760) (**Figure 3**) [9,11]. By the end of 2011, urban residents increased to 690.8 million people, or 51.3% of the population [10]. With rapid urbanization, increasing numbers of people are changing their lifestyles in such a way that may promote chronic diseases – such as decreasing their physical activity. Moreover, by 2030, people 65 years and older will account for at least 20% of the population, representing 240 million people [12]. Economic growth, urbanization, and population aging together are expected to contribute to a 40% increase in the non–communicable disease burden by 2030[12]. At the same time, less than half of patients of with hypertension and diabetes are diagnosed and even fewer receive effective treatment [13], suggesting a large and growing need for essential medicines for the treatment of long–term chronic conditions.

Medicines to treat many non–communicable conditions are expected to become more accessible. By 2015, 40% of the current patent–protected products will be developed as generics as the patents expire [14]. This will lead to the increased use of these medicines as generics in China, where they will become more cost–effective for inclusion under public health care benefit packages – and more accessible for patients who pay out–of–pocket.

## THE REFORM OF THE ESSENTIAL MEDICINES SYSTEM

The national health care reform announced in April 2009 focuses on strengthening insurance, public health services, service delivery, public hospitals, and essential medicines. **Table 1** summarizes the policy directions for the main reform components [4,5,15,16,18], and the implications for medicines affordability and access. **Table 2** presents a summary of the essential medicines reforms.

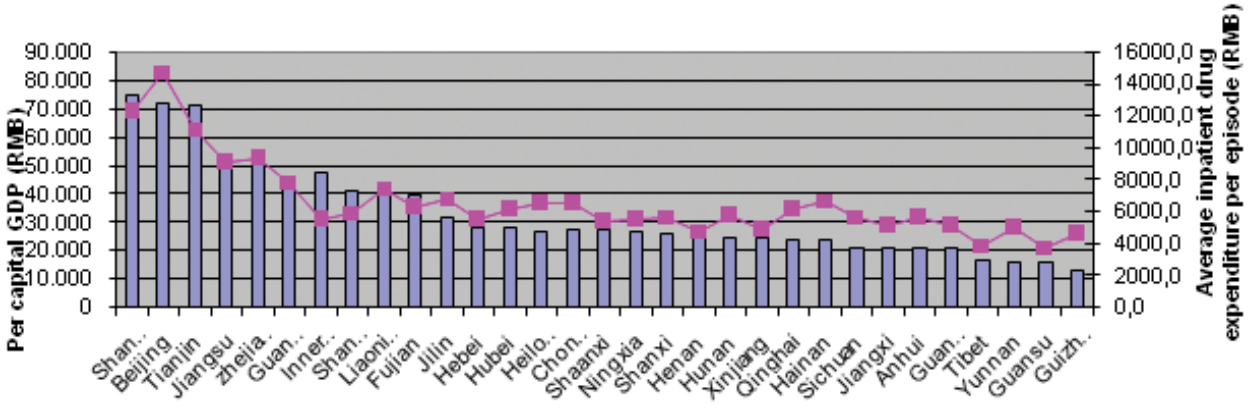



**Figure 2** Per capita GDP and average medicines expenditure per inpatient visit, by region 2010. Source: ref. [10].

## Essential medicines lists (EML)

The Ministry of Health first published its EML in 1982. By 2004, the EML (for primary and secondary levels) included 2033 products, including 1260 Chinese herbal preparations and 773 chemical and biological medicines products. To increase their availability, essential medicines were subject to price controls. However, this had the perverse effect of reducing financial incentives for their production, resulting in the lower availability of highly cost–effective preparations [17]. Until 2009, the EML was not used in financing and insurance reimbursement schemes. With the expansion of coverage and increase in reimbursement levels, the EML has become more important in defining benefits under the insurance schemes.

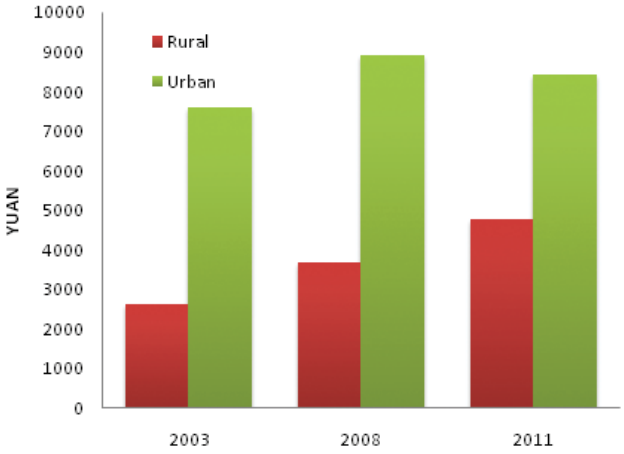



**Figure 3** Average cost of an inpatient visit (Yuan) in rural and urban areas, in 2003, 2008, and 2011. Source: ref. [11].

After health care reform was announced in 2009, the government issued a revision of the first part of the EML for primary care facilities. This EML is currently composed of 307 medicines, including 102 traditional medicines. It is expected that the second part of the EML for secondary hospitals will be issued at a later date. Following the completion of the central list, each province and municipality prepares its own EML. A study of 22 provincial EMLs reported that wealthier provinces added on average 236 medicines to the list, and less prosperous provinces added 107 products [19].

The selection criteria include clinical need, safety and efficacy, price, availability from suppliers, clinical treatment

**Table 1.** National health care reform in China: The impact of health care reforms on access to and utilization of essential medicines*

| Area of reform | Impact on essential medicines |
|---|---|
| **Social security and insurance:** | Large–scale increase in the number of people covered under formal insurance programs, from 294 million in 2003 to 1.28 billion by 2011 (21.0% to 93.0% coverage).<br>Insurance reimbursement lists are required to incorporate the medicines on the Essential medicines lists (EML) at central and provincial levels, at higher reimbursement rates compared with medicines not on the EML.<br>Inpatient insurance reimbursement rates rose steadily, averaging 46.9% in 2011, including medicines and service fees.<br>Per capita premiums for basic health insurance programs to increase to 360 Yuan (US$ 57) per person by 2015, from about US$ 32 in 2010. |
| **Service delivery:** | Reconstruction of the primary care system, including some 2200 county hospitals and 33000 urban and rural primary care facilities.<br>In government–run primary care facilities, comprehensive financing reform under way to replace revenue from medicines sales to fund operational costs, through increased insurance and government subsidies.<br>Greater emphasis on quality, through clinical treatment guidelines, hospital formularies, and prescription monitoring systems.<br>By 2015, the government aims to achieve 90% of outpatient utilization at county level or below. |
| **Public health:** | Ten categories of basic public health services have been implemented, through a per capita subsidy (25 Yuan) to primary care facilities. The subsidy is targeted to increase to 40 Yuan by 2015.<br>The public health subsidy replaces to a large extent the revenue lost through the zero mark–up policy for essential medicines, and covers a large share of operational costs at township hospitals, village clinics, and community health services centers.<br>Eight categories of major public health services, including expanded access to millions for Hepatitis B vaccines and cervical and breast cancer screening. |
| **Public hospital reform on pilot basis:** | 17 municipalities and 37 provincial cities were designated to undertake hospital reform on a pilot basis, to reduce the reliance on medicine sales as a major source of revenues. The main activities include provider payment reform (mainly DRGs and case based payments) and clinical pathways, setting fixed prescription fees, and setting up independent pharmaceutical distribution networks.<br>In 300 county hospitals in 2012, it is proposed to eliminate completely the medicines bonus policy, whereby staff are rewarded for over–prescription. |

*Data sources: refs. [4], [5], [15-17].

**Table 2.** National Health Care Reform in China: Summary of activities under the reform of the essential medicines system: 2009–2011 and directions for 2012*

| Area of reform | Major activity | Major impact |
|---|---|---|
| **Essential medicines lists** | Essential medicines list (EML) for primary level care issued at central and provincial levels. Revisions to be issued in 2012. | Essential medicines available at primary care facilities at cost. |
| **Insurance reimbursement lists** | Insurance reimbursement lists were issued at central and provincial levels, which include the medicines on the EML, at higher reimbursement rates. | Inpatients are reimbursed for essential medicines at higher rates than non–essential medicines. |
| **Procurement** | Centralized procurement and bidding platforms implemented at provincial levels, including online purchasing. Efforts are made to reduce the number of distributors and mark–ups in the distribution chain. The two–envelope system is encouraged, to ensure minimum quality standards under the tendering system prior to consideration of the commercial bid. | Prices for essential medicines have been reduced primarily through greater efficiencies. |
| **Pricing** | Systems have been established for setting and adjusting guiding retail prices for essential medicines. | Through release of pricing data, greater price transparency is possible. |
| **Financing** | Essential medicines are provided at cost (zero profit mark–up) at all government–run primary care facilities in urban and rural areas. Comprehensive financing for primary level facilities to replace revenue from medicines sales, and reform of prices. Zero–mark up will be expanded to village clinics, non–government run primary care facilities, and pilot county hospitals. | Prescribing and physician remuneration/facility operational costs have been delinked at many primary care facilities, thus reducing the incentives for over–prescription. |
| **Quality** | More intensive efforts to improve quality standards for 307 drugs on the national essential medicines list, including routine sampling and testing, electronic bar codes required on packages for monitoring. Strengthened systems for adverse drug effects. | Consumers have greater protection through quality standards, and more confidence in the quality of medicines. |
| **Rational medicines use** | Clinical treatment guidelines and formularies of essential medicines formulated and issued, and prescription monitoring systems put into place. | Increased knowledge of rational medicines use. |

*Data sources: refs. [4], [5], [15-17].

guidelines, and appropriateness for use at primary care level. The selection process for the EMLs and the medicines reimbursement lists, however, is not yet standardized across provinces. The experts participating in the selection may not have access to up–to–date and independent evidence to make informed decisions about cost–effectiveness, safety, and efficacy [19]. In addition, the systems for managing conflict of interest are not yet in place. The process relies primarily on expert opinion rather than objective evidence – which lacks credibility and acceptability among other experts and health professionals that are not involved.

It is tempting to compare the Chinese EML for primary level with the WHO 2011 Model List. However, it is important to recall that the lists serve different purposes. The WHO Model List covers both primary and hospital conditions and addresses some diseases that are not found in China. It includes anesthetic agents, cancer therapies and other medicines that would only be used in hospitals. The WHO Model List does not include traditional medicines.

## Health insurance reimbursement lists

Following the issuance of the EML in 2009, the Ministry of Human Resources and Social Security (MoHRSS) conducted a selection process to issue the central medicine reimbursement list for the urban employee and urban resident insurance programs. The 2009 list includes 2151 products (1164 western and 987 traditional medicines), categorized into List A and List B. All medicines in the EML are in List A, which are reimbursed at higher rates compared with non–essential medicines. The MoHRSS plans to revise the central reimbursement list every four years. Central guidelines indicate that up to 15% of medicines on List B can be adjusted by provinces to meet their own health needs.

While the situation is evolving rapidly, the rural and urban insurance programs focus on the coverage of inpatient care, subject to deductibles and caps. A deductible is the amount paid out–of–pocket by the patient before any insurance payments are paid. For the urban programs, wide variations exist across municipalities, and most municipalities reimburse for primary level outpatient services and medicines depending on their economic capacity. For example, a 2009 study reported that diabetes patients in Huangshui, Hubei, were not subject to deductibles, and were reimbursed at 75% until reaching an annual cap of US$ 267. In contrast, diabetes patients in Shantou, Guangdong, faced a deductible of US$ 158, a reimbursement rate of 50%, and a cap of US$ 952 [20].

Unusually, the EML serves as a minimum list of basic medicines, and the insurance reimbursement lists tend to be much longer compared with the EML. The question is whether funding to "non–essential medicines" diverts resources from other more cost–effective care. Public health benefit and cost–effectiveness could be used in both the selection of the EML and insurance reimbursement lists. Under ideal conditions, the basis for the development of the EML and the insurance reimbursement lists should be evidence–based clinical practice guidelines. Currently, existing clinical practice guidelines and medicines formularies are not widely and consistently used in practice.

## Procurement

Before the reforms, procurement occurred at facility levels; there were many small–scale fragmented distribution systems and large numbers of wholesalers and distributors that contributed to higher mark–ups. The reforms aimed to consolidate the numbers of firms and agencies involved in drug procurement and distribution, reduce costs, and monitor more closely the performance of suppliers. By the end of 2010, government–led bidding platforms were established in all regions, and the majority of counties implemented online purchasing. In general, provincial procurement has promoted greater efficiencies in management. These efficiencies combined with higher volume purchasing have resulted in reductions in medicines prices. The government reported that the price of essential medicines dropped on average by 16.9% between 2009 and 2011 [21]. Independent small–scale studies demonstrated even larger reductions in medicines prices [22]. Yang et al report declines in the average cost per prescription from 45 to 27 Yuan in Hubei province [23].

The central government advocates for the use of the "two–envelope" tendering system, which is under way in some provinces. Under this system, suppliers submit two sets of documents in the bidding process. The first set of documents demonstrates the supplier's compliance with quality and performance standards. For those suppliers that meet the quality standards, the commercial bid is evaluated. However, at present, the procurement process and logistics capacity across the provinces are not uniform; and the systems, specifications, and criteria vary.

Even though large numbers of firms participate in the procurement process, the bidding tends to result in one firm winning the tender for one product. Under most of the current provincial models, the authorities place the strongest emphasis on obtaining the lowest possible price, and pay less attention to medicines quality and reliance supplier performance. This has resulted in price wars among manufacturers, whereby firms submit commercial bids that are below cost. Generally, over–reliance on single–source suppliers may carry risks in decreased competition for certain products. Decreased competition may result in fewer firms registering production and effectively leaving the market. Thus, the system of relying on single–source suppliers could be reevaluated, to ensure that there are sufficient suppliers in the market to ensure competition and choice.

In some regions, medicines on the provincial EMLs are not easily procured. For example, in Fujian province, 42 products on the EML could not be easily procured. The main reasons include lack of supplier, sole source manufacturers, and firms' non–acceptance of the tendering price. In all regions, procurement authorities conduct negotiations among sole source suppliers for products on the EML that are not easily procured.

## Pricing

The Provincial and National Development Reform Commissions (NDRC) regulate prices for approximately 2700 items, among the estimated 11 000 medicinal products marketed in China. Medicines on the central and provincial EMLs and reimbursement lists are subject to price con-

**Photo: Courtesy of Kit Yee Chan, personal collection**

trols, whereby the NDRC establishes maximum retail price ceilings used for procurement and dispensing. Multiple price changes have been introduced for essential medicines since the mid–1990s.

For most essential medicines, NDRC sets the maximum retail prices used for procurement; the actual retail price is determined through competitive bidding by regional authorities and mark–ups at distribution and facility levels. The NDRC collects and verifies data submitted by firms and wholesalers, retail prices from trade associations, provincial procurement prices, and cost studies by manufacturers. There is some variation by type of product, whereby patented medicines, for example, rely on pricing by pharmaceutical companies. In addition, firms that invest in quality improvements and comply with international quality standards – as indicated by an international GMP certification, for example – are eligible to negotiate preferential prices.

The pharmaceutical pricing policy in China contrasts with policies adopted in other countries in several ways. First, it relies on cost–plus accounting methods for pricing rather than commonly used methods used in other countries, such as international benchmarking, internal reference pricing, or pharmacoeconomic analysis. Second, it regulates prices for both branded single–source and generic multi–source products. Many countries rely on market controls for generic multi–source products that can be procured through tendering where sufficient market competition exists. Third, pricing information is generally not made available to the public, although retail medicines prices are available at public health institutions. Finally, a 17% Value Added Tax (VAT) is applied to all medicines, which is relatively high in comparison with OECD countries [24].

In the next 5–year plan, the government intends to strengthen price transparency and disclosure. This is an important step given that greater price transparency at all stages of the medicine supply chain could reduce extreme price variations. Strategies to increase price transparency has been successful in countries such as Brazil, for example, where public procurement authorities can increase their bargaining power by knowing whether prices are competitive [25].

## Comprehensive reform of primary care facilities

Great efforts have been made to encourage utilization of essential medicines and services at primary levels. Making essential medicines available at procurement cost (the zero mark–up policy) was one of several strategies to strengthen the primary care system, alongside infrastructure investments and deployment of qualified health workers [26]. However, the increases in outpatient utilization during the reform period are modest relative to the large increases in inpatient admissions reported since 2003 (**Figure 4**).

At present, there is no separation between prescribing and dispensing, and both are done within the same public health facilities. To reduce the cost of medicines, they are sold at cost in all public primary level facilities. This policy has now been implemented in all government–run primary level facilities. The share of government subsidies to support operational costs at grassroots facilities has increased steadily to compensate for the reduction in revenues from medicines sales. Local governments are mainly responsible for replacing the revenues lost through the zero mark–up policy. In some cases, provincial or central government support is weak, thus placing high financial pressures on local governments, particularly in poor and near poor regions. Insufficient government subsidies may result in shortages in routine operational activities, weak ability to maintain the essential medicine system, or sales of diagnostics, technologies, or other revenue generation methods to cover basic operational costs.

Local governments determine whether to implement a companion policy, to separate revenues and expenditures in government–run primary health institutions. In this model, medicines sales revenues are returned to the county finance department. The institutions are then allocated budgets based on actual costs. In many facilities, however, partial or no separation of revenues and expenditures occurs. Thus, the allocation of government subsidies continues to be based on prescription volumes and represents only the lost profit mark–up. In this case, associations remain between health provider remuneration and volumes of services, diagnostics, and imaging, and the incentives for over–prescription are the same as before the reform.

## Ensuring medicines quality

Under the reform targets for medicines quality, the government put into place stronger production standards, safety

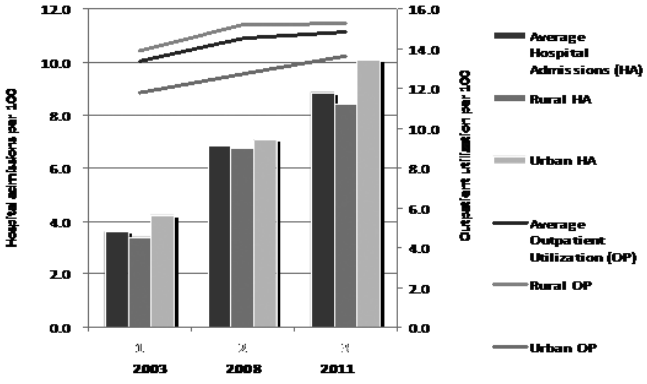



**Figure 4** Increases in outpatient utilization (lines) and hospital admissions (bars): 2003, 2008, and 2011. Source: ref. [11].

regulations, and post–marketing surveillance. The key achievement was the implementation in 2011 of the revised Good Manufacturing (GMP) standards, which do not differ in any critical ways from the WHO GMP standards. It is anticipated that GMP implementation will result in consolidation across some 4600 manufacturers registered to produce finished pharmaceutical products (FPPs) and/or active pharmaceutical ingredients (APIs) [27].

Since 2000, a series of government policies were put into place to promote higher quality standards [28]. A persistent problem has been the quality standards for traditional medicines [29]. In 2011, the government announced strengthened regulations to promote quality in the production, sales and use of prepared slices of Chinese crude medicine. Since 2009, all medicines on the essential medicines list (EML) are required to undergo quality sampling and testing at provincial level annually, and at central level every three years. Substantial numbers of TCM injectables are included on the central and provincial EMLs, and these products pose the highest safety risks. Thus, greater attention to the highest risk products is warranted.

The majority of the medicines on the list are generics. At present, generic products can be used as comparators for generic medicine approvals, where an originator product is not available. This may lead to lack of inter–changeability across generic products, and between generics and the originator products.

## DISCUSSION AND CONCLUSIONS

The implementation of the WHO essential medicines concept is intended to be flexible and adaptable to many situations. The Chinese reforms were grounded in the WHO concept of Essential Medicines established in 1975 by the World Health Assembly, which aims to ensure medicines access and affordability, rational use, and quality and safety[30].Policies have been implemented to promote the availability of essential medicines of assured quality at affordable prices. The essential medicines reform is comprehensive and includes systematic selection of essential medicines, centralized procurement and tendering at provincial levels, pricing policies, provision of essential medicines at cost in primary level facilities (zero mark–up), and stronger quality and safety standards. A great deal of progress has been achieved within a short timeframe. The health reform implementation plan for 2011–2015 has set forth activities to consolidate and expand on these gains [18]. This systematic and comprehensive approach applied in China serves as a useful model for other countries in reforming its health care system.

A few challenges remain. It is essential to accelerate the introduction of a scientifically robust system of inter–changeability of generics, which would pave the way towards comprehensive policies to promote the use of generic medicines. The development of objective and evidence–based clinical guidelines remains an important yet neglected part of the reform. Under ideal conditions, the basis for the development of the EML and the insurance reimbursement lists should be evidence–based clinical practice guidelines. Information required for developing evidence–based guidelines includes current utilization patterns for services and medicines. Practice guidelines should start with common conditions of public health significance and high usage medicine products. Reimbursement lists should utilize the same information, and financial incentives could be provided to promote utilization at primary levels and essential medicines. Where guidelines are used as the basis of public funding, it is important that the process of guideline development is consistent with international standards.

In terms of procurement, provinces will need to adopt stronger and more uniform criteria to accurately capture product quality and firm performance in contract delivery. Consideration could be given to different types of price setting mechanisms to ensure that prices are set with some reference to their therapeutic value. In addition, price controls need to address the mark–ups and VAT, and also the volumes prescribed. Consumer education is an essential part of successful essential medicines policies, to ensure that consumers understand and trust essential medicines. Patient and consumer education should be incorporated into the national policy framework.

Under the current system, increased use of essential medicines relies on the shift in patient care seeking behaviors from hospitals to primary care facilities. This shift will require improving quality of care and human resources at the primary level, and aligning the incentives in the insurance systems to promote referral systems. Piloting alternative ways of paying health care providers is under way across China, and an expansion of these pilots is envisioned.

It is quite early in the reform process to expect major changes in medicines spending. However, this paper illustrates a complex sequencing of events, whereby the institutional structures and policies are put into place first, complementary reforms including insurance expansion are under way at the same time, and comprehensive monitoring systems are established to enable adjustments along the way.

In China, a comprehensive approach to implementing the essential medicines concept was required given that medicines sales were the basis for operating costs for health facilities. The reform in essential medicines is linked closely with the success of improving quality of primary care facilities and implementing public hospital reforms. The comprehensive approach to implementing the essential medicines concept in China is useful for other coun-

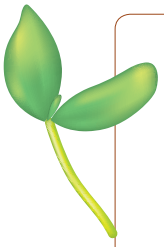
tries that seek to achieve universal coverage, and ensure medicines access and affordability, rational use, and quality and safety.

## What we already know about the topic concerned

The problems of access and affordability in China's health system have been well documented [31]. The ambitious design and objectives of national health care reforms in 2009 were publicized [4,5]. Existing studies and reviews have documented trends in access and financial protection, with a focus on insurance reforms, access, and the increase in spending on health [9]. It has been documented that a large share of total health spending is dedicated to pharmaceuticals, amounting to 2.1% of GDP [7]. Prior studies of essential medicines in China have focused on narrow aspects such as production quality [28] and the selection process for the essential medicines list [19].

## What new knowledge the manuscript contributes

This manuscript provides a comprehensive description of the large–scale essential medicines reform under way in China. To the authors' knowledge, no prior detailed description of activities under this reform component has been published previously. Given that medicines have long been used to fund operational costs for health facilities, reform of the essential medicines system can have a far–reaching impact on access and quality of health services. The comprehensive approach is an excellent example of adaptation of the WHO Essential Medicines Concept, which can be informative for other countries.



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# Helping Haiti's transportation issues: Increasing Haiti's medical liabilities

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Recently, I went on my first medical mission to Les Cayes, Haiti. I was amazed and astonished at the number of Haitian's riding motorcycles. However, what was even more astonishing was the lack of safety that was being practiced by the drivers and passengers. This was compounded by the absence of clear traffic laws to govern the use of automobiles and motorcycles alike. I did not realize the gravity of the issue until we got on ground at our medical clinic and started treating patients. One after another, patients arrived with multiple injuries from motorcycle accidents. Some accidents resulted in minor lacerations while others ended with extensive orthopedic injuries and death. After leaving the country, I thought extensively on how this one problem, which greatly impacted the Haitian medical system, could be improved. There are some simple fixes to this issue like providing operators with motorcycle helmets to more extensive remedies such as establishing and enforcing national transportation laws. Nonetheless, I kept coming back to the same question: How did the people of Haiti get to where they are today with an abundance of motorcycles abound and safety measures lagging far behind?

## BACKGROUND

As the poorest country in the western hemisphere and among the poorest in the world, Haiti does not have the infrastructure for a modern working public transportation system [1]. The transportation issues that were present in Haiti only worsened after the horrific earthquake that occurred in Haiti on January12, 2010. The devastating earthquake killed close to 300 000 people and injured hundreds of thousands more. The international community besieged the airport in Port–Au–Prince with equipment to help in the recovery and reconstruction efforts in Haiti. Many roads were so badly damaged that vehicles were unable to navigate them or became damaged themselves as a result. Therefore, many aid agencies began to bring motorcycles into the country to help navigate the treacherous roads. These motorcycles were essential in providing food and medical aid, and in moving people not only throughout Port–Au–Prince and into surrounding villages. Furthermore, organizations such as The Christian Motorcyclists Association distributed motorcycles to pastors so they could provide essential spiritual support to those in hard to access regions [2].

Other aid agencies have similarly utilized motorcycles to distribute medicine and transport patients needing medical care. United States aid agency "Save the Children", found the country side of Somalia littered with abandoned motorcycles left by earlier aid workers who did not know how to maintain their equipment [3]. The agency paired with Riders for Health to maintain the bikes and train riders to utilize the motorcycles to improve Somalia's medical system

Haiti has experienced an explosion of the use of motorcycles by young, inexperienced drivers fueled by the departure of aid workers leaving them behind after assisting with disaster relief. The consequence is a strain on Haiti's already fragile medical system due to the overwhelming number of traumas presenting for treatment. The motorcycles have become an indispensible form of transportation but lack of governmental oversight predisposes an environment that is primed to strain the country's already limited medical assets.

by transporting medicine, patients and health care providers. Riders for Health has expanded its work and implemented similar programs in Uganda, the Gambia, Ghana, Zimbabwe and Nigeria implementing programs in countries with a transportation infrastructure similar to Haiti's.

As recovery efforts in Haiti have wound down, many of the aid organizations left behind the motorcycles that were so crucial in aid efforts after the earthquake. Abbot, after her first trip back to Haiti after the earthquake, stated that "the contingent that really caught my eye was the army of young males on motorbikes, riding with the cockiness of immaturity exacerbated by the frustration of travel on Haiti's miserable roads." [4]. Abbot continues [4]:

**Photo: Courtesy of MaryAnn Reuben, personal collection**

> "Many of them operate as unofficial taxis, transporting customers one by one. In a country near infrastructural collapse, they are an important part of the private sector – and only – transportation system. As part of their scramble to pay for and fuel their bikes, they offer an affordable service that on mountainous Haiti's twisting, gutted roads, is often the only alternative to drudging on foot or mounting the rubbed–raw back of a thirsty, overburdened mule or pony."

Passengers are not afforded the luxury of motorcycle helmets nor do the driver's wear any type of protective gear. When speaking to many young men who drive these motorcycles, they almost unanimously stated that they probably would not wear a motorcycle helmet even if given one. This reminds me of a time in the United States when seatbelt laws were being enacted. Many people would not wear the seatbelt, although it had become a law, because it was not "cool" to wear one.

The problem of immature motorcycle operators is only compounded by the abysmal road conditions still present in Haiti, as well as the lack of basic traffic laws. There is no national system to maintain the roadways that are currently present in Haiti. Furthermore, there is limited access to the asphalt needed to repair roadways. Rain, especially during hurricane season, wreaks havoc on the existing roads, making them slippery and muddy, as they are not engineered to facilitate runoff. Traffic lanes are frequently undesignated and populated by pedestrians, livestock, and vendors and guard rails, stop signs, stop lights, and speed limit signs are visibly absent. Drivers often wear headphones to listen to music instead of observing their surroundings and driving defensively, and of course many vehicles are poorly maintained making them a hazard to their operators and others on the road. All of these issues, coupled with immature and reckless operators, cause many otherwise preventable accidents.

## BURDEN ON THE ALREADY STRAINING HEALTHCARE SYSTEM

Haiti's health care system was poor prior to the earthquake in January 2010, and certainly is in a shambles after it. In Haiti, where the average person makes just over US$ 1 a day, expensive, inaccessible health care can often make the difference between life and death [5]. Even though the Haitian constitution has provisions for universal health care, the reality that health care is easy to access is a farce. Crane et al. note [6]:

> "Forty percent of the population lacked access to care, particularly in rural areas of the country. Lack of access has two dimensions: lack of physical access, as 13 percent of the population lives more than 15 kilometers away from the nearest health center, and lack of financial access, as cost–recovery policies in place in most institutions require fees for services that are unaffordable to a large proportion of the population."

Conditions are rarely treated in a timely manner, which only compounds their severity and increases the morbidity and mortality rates.

Even if Haitians could readily access facilities and had the financial means to pay for care, they would have to face the challenges of finding qualified physicians and nurses. While current numbers for physician density in Haiti are

I did not realize the gravity of the issue until we got on ground at our medical clinic and started treating patients. One after another, patients arrived with multiple injuries from motorcycle accidents. Some accidents resulted in minor lacerations while others ended with extensive orthopedic injuries and death. After leaving the country, I thought extensively on how this one problem, which greatly impacted the Haitian medical system, could be improved.

not generally available, in 2001 Haiti had only three physicians for every 10 000 inhabitants; most were concentrated in the capital [6]. In addition, the physical facilities of hospital are dilapidated and experience frequent power outages and water shortages. The equipment utilized to deliver medical care is usually outdated and/or broken. Furthermore, medical facilities often lack the administrative support staff to deliver quality care to those in need.

Haiti's major health problems are similar to those of other third world countries: low immunization rates, high prevalence of vector borne diseases, HIV/AIDS, and high infant mortality rates. These medical conditions all pose a significant strain on the medical assets that Haiti does have to offer. Trauma–related motorcycle accidents are a major issue that is poorly reported by scholarly literature. It only takes a few days on ground in Haiti, providing medical aid to begin to realize that motorcycle accidents tax an already fragile health care system.

## CASE STUDY

A 35-year old Haitian male presented to the city hospital's emergency department on Wednesday with an open unstable tibia fracture after being hit as a pedestrian by a motorcycle operator who was driving carelessly. He was treated with pain medication, a long leg posterior splint, given a prescription for antibiotics and analgesics and told to return to the hospital courtyard near the operating room the next day to see if he would be able to have surgery. He was unable to purchase both the analgesics and the antibiotics; therefore, he chose the analgesics. He was told to return to the hospital courtyard near the operating room the next day to see if he would be able to have surgery. He waited all day Thursday but was unable to have surgery because an orthopedic surgeon was not available. He returned on Friday and once again waited but was unable to get surgery. At this time, blood had soaked his dressings and there was no projected date at which he would be able to undergo surgery.

In comparison, this same injury would have been treated in a dramatically different way in the United States. Open fractures often become contaminated; therefore great diligence is paid to prevent infections which are preempted by devitalized bone and soft tissue. The main treatment goals are: limb salvage, prevention of infection, and restoration of function. Therefore, open fractures also require administration of tetanus prophylaxis and intravenous antibiotics with a cephalosporin, such as cefazolin, which would require an inpatient admission [7]. Consequently, a fracture such as this would typically be taken to the operating room very early after the incident and an intramedullary nailing would be performed to stabilize the fracture. Delay in the treatment could result in osteomyelitis, amputation, or even death.

## CONCLUSION

In a case like Haiti an ounce of prevention is worth a pound of cure. Educating inexperienced motorcyclist will be the challenge. Motorcycle safety is undoubtedly one of the last things that cross a driver's mind until he is involved in an accident. Because of infrastructural limitations, the actual burden placed on the Haitian medical system by these medical emergencies is hard to estimate, but anecdotally any health care provider who has spent time in Haiti will tell you that this is a major issue. Without governmental intervention and enforcement of traffic and safety laws, there is no real way to decrease the number of trauma related to motorcycle accidents.

Other developing countries face the same problems as Haiti. Iamtrakul et al. completed an extensive analysis of traffic accidents involving motorcycles in Thailand and the outcomes of the patients [8]. Their work showed the following results: 1) men had twice as many motorcycle accidents as women, 2) the severity of men's over women's injuries were twice as great, 3) accident severity of drunk drivers was four times higher than normal drivers, and 4) drivers not wearing helmets had 6 times greater severity of injuries over those patients who were wearing helmets at the time of their accident. A Nigerian study showed that motorcycles are often useful for navigating poor roads and traffic hold–ups, but the riders often ignore safety measures, making them more vulnerable to accidents [9].

Governmental intervention would have to occur on multiple levels. Instituting just a few of the following prevention strategies would greatly decrease the burden on the health care system. First, riders need to be educated about personal protective gear that could be worn to help prevent injury. Obviously, a mandatory helmet law would be a huge

step in the right direction. Solagberu et al. [9] noted that studies have shown that "limb and head injuries are the most common causes of morbidity and mortality in motorcycle accidents, attributing the latter to low use of crash helmets in Nigeria, a situation seen in other developing countries." This illustrates that the issue of helmet use is not unique to Haiti. Road rules and traffic laws need to be instituted to cut down on the confusion that drivers experience while negotiating Haiti's treacherous roads. Johnson and Adebayo [10] were able to show that basic motorcycle safety classes significantly decreased the morbidity and mortality among Nigerian motorcycle riders. Iamtrakul et al. [8] recommended graduated licensing to combat the issue of young drivers in Thailand. Limiting the number of passengers allowed to ride on a motorcycle at any one time would reduce the potential number of injuries. Basic road maintenance should be performed to help fill potholes and clear debris from the street. Finally, requiring yearly safety inspections of motorcycles would also be useful.

All of the previously mentioned interventions would help to decrease the morbidity and mortality rate that Haiti experiences from the vast number of motorcycle accidents that occur daily. Most of the mentioned interventions require a strong governmental presence, which is currently a challenge to a politically unstable Haiti. In the meantime, the associated trauma that occurs as a result of these motorcycle accidents will only continue to drain the medical assets of an already struggling medical system.

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PAPERS

# Epidemiology and etiology of childhood pneumonia in 2010: Estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries

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**Background** The recent series of reviews conducted within the Global Action Plan for Pneumonia and Diarrhoea (GAPPD) addressed epidemiology of the two deadly diseases at the global and regional level; it also estimated the effectiveness of interventions, barriers to achieving high coverage and the main implications for health policy. The aim of this paper is to provide the estimates of childhood pneumonia at the country level. This should allow national policy–makers and stakeholders to implement proposed policies in the World Health Organization (WHO) and UNICEF member countries.

**Methods** We conducted a series of systematic reviews to update previous estimates of the global, regional and national burden of childhood pneumonia incidence, severe morbidity, mortality, risk factors and specific contributions of the most common pathogens: *Streptococcus pneumoniae* (SP), *Haemophilus influenzae* type B (Hib), respiratory syncytial virus (RSV) and influenza virus (flu). We distributed the global and regional–level estimates of the number of cases, severe cases and deaths from childhood pneumonia in 2010–2011 by specific countries using an epidemiological model. The model was based on the prevalence of the five main risk factors for childhood pneumonia within countries (malnutrition, low birth weight, non–exclusive breastfeeding in the first four months, solid fuel use and crowding) and risk effect sizes estimated using meta–analysis.

**Findings** The incidence of community–acquired childhood pneumonia in low– and middle–income countries (LMIC) in the year 2010, using World Health Organization's definition, was about 0.22 (interquartile range (IQR) 0.11–0.51) episodes per child–year (e/cy), with 11.5% (IQR 8.0–33.0%) of cases progressing to severe episodes. This is a reduction of nearly 25% over the past decade, which is consistent with observed reductions in the prevalence of risk factors for pneumonia throughout LMIC. At the level of pneumonia incidence, RSV is the most common pathogen, present in about 29% of all episodes, followed by influenza (17%). The contribution of different pathogens varies by pneumonia severity strata, with viral etiologies becoming relatively less important and most deaths in 2010 caused by the main bacterial agents – SP (33%) and Hib (16%), accounting for vaccine use against these two pathogens.

**Conclusions** In comparison to 2000, the primary epidemiological evidence contributing to the models of childhood pneumonia burden has improved only slightly; all estimates have wide uncertainty bounds. Still, there is evidence of a decreasing trend for all measures of the burden over the period 2000–2010. The estimates of pneumonia incidence, severe morbidity, mortality and etiology, although each derived from different and independent data, are internally consistent – lending credibility to the new set of estimates. Pneumonia continues to be the leading cause of both morbidity and mortality for young children beyond the neonatal period and requires ongoing strategies and progress to reduce the burden further.

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Pneumonia is still the leading cause of child mortality globally [1,2]. However, an increased focus on the reduction of child mortality that arose from the United Nation's Millennium Declaration [3] and the Millennium Development Goal 4 has renewed the interest in developing more accurate estimates of the causes of child deaths. This should inform more effective health policies and track the progress of their impact. In 2001, the Child Health Epidemiology Reference Group (CHERG) – a group of independent technical experts funded by The Gates Foundation and working closely with the World Health Organization (WHO) and UNICEF– set out to systematically review and improve data collection, methods and estimates of the main causes of child deaths for 2000 [4]. Evidence from CHERG estimates – ie, that pneumonia was the leading cause of child mortality – contributed to the initiation of a number of global efforts, such as the Global Action Plan for Pneumonia (GAPP). GAPP was designed to promote the expansion and improvement in community case management, the reduction in risk factors for disease and the support for the massive roll–out of vaccination against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* (SP) by countries through support from the GAVI Alliance [5,6]. Those efforts, alongside economic and social developments observed in many low– and middle–income countries over the past decade, have all contributed to a substantial reduction of the burden of morbidity and mortality from childhood pneumonia [7].

CHERG's work also led to several Lancet series that had a substantial impact on global, regional and national–level donors and policy–makers [7–10]. It also inspired similar efforts to address the epidemiology and provide estimates for other causes of the global burden of different diseases [11,12]. The recent series of reviews published in the *Lancet* and *PLoS Medicine*, conducted by CHERG members in collaboration with the WHO, UNICEF and USAID within the Global Action Plan for Pneumonia and Diarrhoea (GAPPD), addressed the epidemiology and the current global burden of the two leading causes of childhood death, pneumonia and diarrhea, in the year 2010–11 [13]. The series also estimated the importance of risk factors [13], effectiveness of interventions [14], barriers to achieving high coverage at the community level [15], validity of coverage measures [16–17] and main implications for health policy [7].

The recent GAPPD reviews focused at the global and regional level [13]. The aim of this paper is to supplement the *Lancet*'s GAPPD series with further information on the underlying models and methods, to augment that already available, and thereby assure that all input data and detailed descriptions of methods are transparently presented and available in an open–access source. Additionally, this paper also provides estimates of childhood pneumonia burden at the country level to allow national policy–makers and other stakeholders to implement the proposed policies in the World Health Organization (WHO) and UNICEF member countries.

## Challenges to estimation of childhood pneumonia burden

**Incidence and severe morbidity.** An accurate estimate of the global, regional and national burden of childhood pneumonia is very difficult to make for a number of reasons. First, the incidence of pneumonia can only be properly assessed through longitudinal community based studies [18]. Such studies are very scarce in low and middle–income countries, where the majority of the pneumonia disease burden occurs, in part because they require a major commitment from both the investigators and research funders in a low–resource setting over an extended period of time. Due to the seasonal nature of pneumonia incidence, which has various peaks in different seasons, studies measuring incidence need to be conducted over full calendar years (or multiple 12–month periods) [19]. The screening of large numbers of children needs to be active, regular and frequent (eg, no longer than 2 weeks between home visits), because recall bias leads to under–estimation especially in large families [19]. In addition to these basic methodological requirements, the most fundamental uncertainty with measuring the incidence of childhood pneumonia in a community setting comes from the choice of case definition and the accuracy of its application by the assessor who establishes the diagnosis. Since pneumonia is actually a diagnosis made on tissue pathology, there is no clinical definition that is fully accurate. In any community–based study on pneumonia incidence, the measured entity is not in fact childhood pneumonia itself, but rather the incidence of children who test positive for the chosen case definition of childhood pneumonia [20]. The case definition is based on a number of symptoms and signs; although the WHO definition of childhood pneumonia (cough or difficulty breathing and an elevated respiratory rate, defined according to the child's age) is the most frequently used in field studies, other definitions are often encountered in the literature confounding cross study comparisons of incidence. Depending on the combination of sensitivity and specificity of the chosen case definition, the burden of "true" pneumonia in the community of children can be grossly over– or underestimated [20].

A further problem is that the clinical training of assessors differs between the studies and this often affects the application of case definitions, unless the study implementation is highly controlled. Physicians tend to use their own clinical judgment in addition to the case definition. They will be likely to provide more conservative estimates, while community health workers may over–diagnose pneumonia in a community to the level where they consider a high proportion of acute respiratory infections in a child as cas-

es of "pneumonia" [19]. Moreover, it is important to understand for each study whether the investigators attempted to exclude cases of respiratory disease that met the clinical pneumonia case definition but were assessed in some other way as being bronchiolitis, pertussis, measles, or even asthma, malaria or neonatal sepsis.

The effect of these challenges was reflected in the first–ever attempt to estimate the incidence of childhood pneumonia, which identified only 28 studies that met the minimum quality criteria [18]. The incidence of pneumonia reported in these studies still ranged 100–fold between their minimum and maximum reported incidence rates per child–year which could reflect true heterogeneity in the burden of disease or more likely also reflects the challenges of standardizing the epidemiologic study design and its application at the field level [18]. Similar, if not greater problems are encountered with estimating the incidence of severe, life–threatening pneumonia (which requires hospital referral and treatment) in the community. This estimate cannot be based on measures of childhood pneumonia hospitalizations because parents' care seeking behavior, access to hospitals, and medical professionals' threshold for admission varies widely within and across geographic settings [19]. There are WHO definitions for severe pneumonia (cough and difficulty breathing with lower chest wall indrawing) and for very severe pneumonia (cough and difficulty breathing with danger signs). These definitions are useful insofar as they are applied at the community level for guiding the case management and referral of children to a hospital, hence are purposefully highly sensitive and poorly specific for truly life threatening disease. Therefore, estimates of the incidence of severe childhood pneumonia in the community are particularly rare. Moreover, great caution must be applied in making comparisons between studies or in combining data across studies to assure that only similarly designed and implemented case definitions are considered together. The best estimates of pneumonia usually come from the control arms of randomized controlled trials of vaccines. This is because severe pneumonia is usually an outcome that is being monitored over a multiple of 12 months, usually with a highly stipulated and rigorously implemented case definition. Such studies provide the best estimates of severe pneumonia in the community that we have today [19].

**Mortality.** Estimating mortality that results from childhood pneumonia in a community also has its significant methodological challenges. Mortality studies require similar study designs to incidence studies, although home visits do not need to be as frequent as in the former, because care–giver recall of a child death is more accurate and long–lasting than of an illness episode [21,22]. Identifying the exact cause of death can be difficult in an appreciable number of cases. The assigned cause of death is usually based on a verbal autopsy provided by a mother or another family member. These are typically based on the report of signs and symptoms around the time of death. Many of them are not specific to pneumonia, but can also be found in children with other conditions, such as sepsis and malaria. In addition, many dying children have suffered from chronic malnutrition and may have other underlying ailments, such as asthma, metabolic disorders, immunodeficient conditions (HIV), sequelae of previous injuries, chronic diarrhea, or congenital defects [23]. They may develop pneumonia in addition to an exacerbation of another ailment, or have concomitant malaria or diarrhoea. In such cases, it is challenging to assign the death of a child to a single cause through verbal autopsy. Furthermore, the clinical signs and symptoms of a pneumonia death overlap with those of other causes of death such as malaria or measles, hence misclassification errors are significant. Moreover, there are studies that focus exclusively on pneumonia as a cause of death, while others are multi–cause mortality studies, documenting the causes of all child deaths in the community. Typically, studies focused exclusively on pneumonia tend to over–estimate its contribution to overall child mortality [24]. This is because in such studies it is more likely that a number of other underlying causes or immediate causes may be misclassified as pneumonia. Therefore, multi–cause mortality studies are preferred as a source of information to single–cause studies [24].

**Risk factors.** In addition to estimating the incidence, severe morbidity and mortality from childhood pneumonia at the global, regional and national level, it is important to understand risk factors that contribute to the development of childhood pneumonia and that may offer clues to prevention of the disease. However, well–conducted studies of pneumonia risk factors in low resource settings are remarkably scarce. There is wide variation among risk factor studies in their focus, study design and outcome: while some explore risk factors associated with incidence of pneumonia at the community level, others focus on the risks that are associated with progression to severe disease in those who already have pneumonia [1]. A third type of study are those that are hospital–based and investigate risk factors associated with progression to death in a child receiving treatment and compare case–fatality rates among different children [1].

Another methodological challenge is that the most commonly investigated risk factors for disease or for death are commonly identified together among cases. For example, undernutrition, use of solid fuels in a household, crowding, lack of exclusive breastfeeding, low degree of maternal education, limited access to secondary care and passive care–seeking behavior are all often characteristics of poor households, where most of the deaths occur. Because of this collinearity, an assessment of the effect size of any par-

ticular risk factor in isolation from the role of others will likely lead to gross over–estimation of the true effect size [1,18,19]. Therefore, very large prospective studies are required, based on multivariable study designs, to ensure an adequate number of study participants with heterogeneity in the prevalence of risk factors and thereby allow an accurate assessment of the individual role of each risk factor. Very few such studies exist; this is a permanent research priority, because the effect sizes attributable to individual risk factors in different contexts are still poorly understood [1,18,19].

**Etiological agents.** There is a growing need to identify etiological agents that contribute to the disease development at each of the three levels of severity – episodes of community–acquired pneumonia (incidence), severe pneumonia (severe morbidity) and pneumonia deaths (mortality). This is because vaccines are now available to prevent infections with major pathogens, such and *Streptococcus pneumoniae* (SP), *Haemophilus influenzae type b* (Hib) and *influenza virus* (flu), while a vaccine against respiratory syncytial virus (RSV) is also being actively pursued [25–27]. However, precise estimation of the distribution of the episodes, severe episodes and deaths from childhood pneumonia by etiological agent is even more difficult than estimation of the overall disease burden itself, for a number of reasons. First and foremost, the site of infection – the lung –is generally an inaccessible organ that is in constant contact with the external environment through the naso– and oro–pharynx, which are body sites that are sampling and immunologically responding to potential pathogens. Second, the procedures needed to collect specimens from potential cases are ones that usually require a hospital facility, meaning that studies must be done in places where cases have access to a hospital facility. Such studies also require laboratory facilities that can process samples in a timely fashion and can run a multitude of tests to document presence of pathogens in a child [28]. This means that they tend to be (teaching) hospital–based and therefore do not sample across the whole range of pneumonia cases in a population. Most deaths from pneumonia occur in places where no hospital facility is available, highlighting the nearly inextricable paradox that appropriate studies cannot be done in the places where most of the death burden occurs.

Third, accepting that paradox, even in settings where studies can be done there are further issues. The choice of biological samples (specimen) in which the presence of a potential pathogen should be sought means that multiple body fluids must be collected. Ideally, for a bacterial diagnosis, samples should come from the lung tissue itself (eg, by needle aspirate), from a pleural exudate, or a blood culture sample, but this is often neither feasible nor acceptable in a professional or lay community [28]. As an alternative, analyses of collected sputum or nasopharyngeal swabs can be performed, but their contribution to understanding the etiology is complex since the pathogens identified in these locations are also commonly found among healthy children.

Fourth, the more tests performed, the more agents will be found, and statistical methods to disaggregate and associate individual pathogen contributions to etiology are lacking. This is an increasing problem with modern sensitive techniques like PCR–based tests identifying the presence of often many co–existing and potentially pathogenic agents (whose role in the disease episode is very uncertain). Finally, we don't sufficiently understand the interplay between various pathogens and how a specific time sequence (eg, a viral infection, followed by a bacterial superinfection) may act to compromise the local and/or systemic immune response to cause a serious and life–threatening episode of childhood pneumonia by a pathogen that may otherwise not cause severe disease. Even with sophisticated expansive testing a significant proportion of cases may not have an etiology associated with the case. The meaning of this has to be assessed. Some of these cases may not have pneumonia at all, while other cases may not be associated with an etiology because of statistical methods used, in spite of identification of pathogens in the upper respiratory tract; finally, some may not be assigned to a causal pathogen because of laboratory test insensitivity. There remains therefore a gap in understanding the etiological spectrum of what is clinically defined as pneumonia [25,28].

These complex issues for studying pneumonia etiology are being addressed in a large, 7 country pneumonia etiology study among children (PERCH) [25]. This study is under way and the first results are expected following the completion of the field work (in early 2014) and an analysis period.

Because of the many biologic, epidemiologic, laboratory, and statistical challenges of pneumonia etiology observational studies, the most reliable methods for estimation of the proportional contribution of different pathogens to the burden of childhood pneumonia are vaccine trials [29]. The observed reduction in the incidence of pneumonia (using various case definitions) following vaccination reveals the disease burden attributable to that specific pathogen, once the less than 100% vaccine efficacy of the product is accounted for. This approach also has its limitations, mostly insofar as a vaccine trial can only reveal the burden of one pathogen at a time. For some pathogens (such as SP), not all disease–causing strains may be included in a strain specific vaccine [30]. If the distribution of strains varies by factors that also contribute to variation in pneumonia disease burden (eg, geography, pneumonia case definition, malnutrition, HIV), then careful attention must be paid to applying the vaccine efficacy measures to the appropriate measure of pneumonia disease burden [29]. Also, vaccine–

based approach may be very useful in understanding the causal contribution at the level of incidence and severe morbidity, but may be limited in their ability to inform about the pathogen contribution to mortality (which is often a rare event in vaccine trials, where enormous resources are in place that themselves reduce the risk of death). Finally, although it might be ideal to conduct vaccine trials in parallel in many geographic regions using a harmonized protocol to reveal the geographic variability in contribution of pathogens to disease, vaccine trials are not usually designed for the purpose of disease burden estimation; they are also very expensive to conduct, which limits the number of sites where they can be undertaken [31]. They are generally not sufficiently large to have acceptable statistical power to detect a mortality reduction, as there are relatively few deaths in the study population.

Moreover, after a definite proof of vaccine efficacy and effectiveness is established, there are significant ethical issues regarding the conduct of further trials if they necessitate a control arm in which children are not provided what has been shown to be a life–saving vaccine. This self–limits the accumulation of the evidence towards the importance of specific pathogens. An additional layer of complexity comes from the notion that the etiological spectrum may change markedly with increasing severity of disease: at the level of incidence of childhood pneumonia in the community, viral causes seem to be responsible for a majority of episodes. However, a proportion of these cases will result in severe and life–threatening disease. In a sub–sample of severe cases, bacterial agents seem to be over–represented. Evidence from antibiotic treatment trials, from vaccine trials, and from studies of lung puncture studies provide a firm evidence base that episodes of death from pneumonia are dominated by bacterial causes. If true, this would suggest that SP and Hib vaccine probe studies (with "proxy" endpoints of severe episodes prevented) may under–estimate the importance of these agents as a cause of death. Longitudinal studies of mortality in low–income countries that have introduced Hib and SP vaccines recently and that are achieving high vaccine coverage will likely provide confirmatory evidence of that contribution to pneumonia mortality in the coming years [25,26,31].

## An overview of previous estimates

One of the earliest attempts at estimating the global burden of communicable diseases was provided by Cockburn and Assaad in the early 1970s [32]. Bulla and Hitze built on their work by specifically addressing the contribution of acute respiratory infections [33]. Almost a decade later, Leowski [34] used data from 39 countries to estimate that acute respiratory infections may have been causing about 4 million child deaths each year: 2.6 million in infants and further 1.4 million in children aged 1–4 years. In the early 1990s Garenne et al. [35] further refined these estimates using an epidemiological model that explored the association between all–cause child mortality and the proportion of deaths attributable to acute respiratory infections, showing that between 20–33% of child deaths were associated with respiratory infections [35,36].

The 21st century has seen a much larger number of efforts, mainly designed and led by CHERG and their partners, which further improved the understanding of the epidemiology and etiology of childhood pneumonia. The first estimate of global incidence of childhood pneumonia was provided by Rudan et al. [18] for 2000. In parallel, a refined estimate of childhood pneumonia mortality for the same year, based mainly on single–cause studies, was provided by Williams et al. [37]. The first estimate of pneumonia mortality from multi–cause studies was published by Black et al. in CHERG's paper on the causes of global child mortality in the year 2000 [4]. Then, estimates underwent further refinements and updates. An updated estimate of childhood pneumonia mortality for 2008 in post–neonatal children in low and middle–income countries, based on single–cause studies, was provided by Theodoratou et al. [38]. Estimates based on multi–cause studies underwent three updates: for the period 2000–2003 by Bryce et al. [39]; for 2008 by Black et al. [40]; and for 2010 by Li et al. [41].

The first comprehensive assessment of the burden of severe pneumonia according to the WHO's definition and the role of risk factors was provided by Rudan et al. [1,18]. This work was followed by the first attempt to estimate the global burden of childhood pneumonia on health systems; Nair et al. [42] used both published and unpublished information to calculate the number of hospitalizations for severe pneumonia, a number which is smaller than the estimate of cases of severe pneumonia in the community because of lack of access and/or care–seeking in many settings.

Once the "envelopes" for the burden of pneumonia incidence, severe morbidity and mortality from pneumonia in 2000 were provided, a series of efforts attempted to estimate the proportion of the burden at each level of severity that can be attributed to the main etiological agents that cause pneumonia. O'Brien et al. [43] developed the first global, regional and country estimates for the morbidity and mortality from *Streptococcus pneumoniae*, Watt et al. for *Haemophilus influenzae* type b [44], while Nair et al. generated global and regional estimates for RSV [45] and for influenza [46].

The estimates of pneumonia incidence, severe pneumonia cases, severe pneumonia hospitalizations, pneumonia mortality, and cause specific estimates are based on different and almost entirely independent sources of information, which allows for assessments of validity and consistency

between the various estimates. Validation of these estimates can be approached in various ways. A few examples include: (i) an assessment of the measured proportion of all pneumonia cases that are categorized as severe; (ii) the ratio between the estimates of severe episodes and deaths, and also (iii) between all pneumonia episodes and deaths. These proportions and ratios need to largely support the observed case–fatality rates typically seen in both community–based and hospital–based data sets from individual studies. Moreover, the sum of etiology specific fractions attributed to different pathogens needs to fit within the overall burden of incidence, severe morbidity and mortality. For the Hib and pneumococcal pathogen specific estimates, they must fit within these envelopes by definition, since the methodology to estimate the absolute burden was a proportional approach – but this was not the approach for the estimation of the RSV or influenza burden. The ratios between different pathogens were also found to broadly reflect those observed in the high quality field studies or hospital–based studies further validating the estimates. Towards the end of the past decade it was notable that, regardless of all methodological challenges and uncertainty inherent to this research, all the major estimates from different sources were increasingly consistent with each other and provided a clearer global and regional picture of the burden of childhood pneumonia and its causing pathogens, albeit with wide uncertainty bounds around the point estimates [40–46]. This paper therefore brings all the estimates together and provides an update for 2010–11, in which all information is provided in a single analysis, and where country–level estimates are also be provided.

## METHODS

Many steps are required to develop an internally consistent estimate of global, regional and national burden of childhood pneumonia based on best available evidence. To fully explain our approach, we developed a table (Online Supplementary Document) which all input data, assumptions, methods, solutions to specific problems or dilemmas, formulae for calculation of different parameters, and the interim and final estimates are provided. In this section, we present a summary for those steps, list all sources of data and explain the rationale for each subsequent step.

### Input data for country–level populations and prevalence of risk factors for pneumonia incidence

Initially, we list 192 countries by World Health Organization's regional classification, with 6 main regions (the Americas (AMRO), Africa (AFRO), Eastern Mediterranean region (EMRO), European region (EURO), Western Pacific region (WPRO) and South–East Asian region (SEARO)) and further divisions by the level of development into "A", "B", "C", "D" and "E" sub–regions [47]. For each country, an estimate of the population of children under the age of 5 years in 2010 was obtained from the UN's Population Division [48]. Then, the 5 most important risk factors for childhood pneumonia incidence were identified. They were selected based on consistently significant effects in multivariate study designs and previous meta–analyses [1,18]. They are: malnutrition (weight–for–age $z<-2$), low birth weight (≤2500 g), non–exclusive breastfeeding (in the first 4 months), solid fuel use ("yes") and crowding (7 or more persons sharing the same household) [1,18]. The data on the prevalence of exposure to each of those 5 risk factors in each country in the year 2010(or the closest year with available data) was obtained from the recent Demographic and Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS) [49,50]. For all countries in which data on the prevalence of exposure were not available, the prevalence was imputed based on the regional mean value, which was weighted by population size of all countries with any data. The effect size of each risk factor on pneumonia incidence was assessed through meta–analysis of the studies that reported multivariable analyses of risk factor's odds ratios (OR) in low and middle–income countries. The meta–estimates of odds ratios assigned to each risk factor were: 1.8 for malnutrition, 1.4 for low birth weight, 1.3 for non–exclusive breastfeeding, 1.8 for use of solid fuels and 2.0 for crowding. In high–income countries, where less than 2% of all cases of community–acquired pneumonia occur, we did not use the model based on risk factors but rather applied "flat" rates of incidence for "A", "B" and "C" regions based on several high–quality studies (see Online Supplementary Document), and which ranged between 0.015 and 0.060 episodes/child–year (see later). For the proportion of severe episodes in each high–income region we used one single rate which was the median of all available studies (26.7%, see later).

### Computation of country–level incidence of pneumonia and severe pneumonia

In all LMIC countries, we multiplied the number of children in each country by the prevalence of exposure to each of the 5 risk factors. This provided an estimate of the absolute number of exposed children in each country who were at excess risk of developing childhood pneumonia in the year 2010. We then calculated the proportion (ie, a weighted mean) of all children in each LMIC region and country exposed to each of the 5 risk factors; then, in each country, we multiplied the proportion of children who were above, or below, the regional exposure level with the meta–estimate of the odds ratio attributable to each of the 5 risk factors.

The number of pneumonia cases in each low and middle–income country (LMIC) was calculated using a model

based on the epidemiological concept of potential impact fraction [51], as follows:

$$N = \left(Pop_{<5yrs}\right) \times \left(Incl_{LMIC}\right) \times \left\{1 + \Sigma_{(RF=1 \rightarrow n)} \left[\left(\text{Prev}_{RFn} - \text{Prev}_{\text{RFnLMIC}}\right) \times \left(RRR_{Fn} - 1\right)\right]\right\}$$

where N is the number of new episodes of childhood pneumonia per year in each country, $Pop_{<5yrs}$is the population of children aged 0–4 years in each LMIC, $Inc_{LMIC}$ is the estimated incidence of clinical pneumonia for all LMIC, $Prev_{RFn}$ is the prevalence of exposure to *n*–th risk factor among those under 5-year in the country of interest, $Prev_{RFnLMIC}$ is the prevalence of exposure to $n^{th}$ risk factor among under–fives in all LMIC, and $RR_{RFn}$ is the relative risk for developing clinical pneumonia associated with the $n^{th}$ risk factor (see Online Supplementary Document for further details).

The incidence of pneumonia for all LMIC was derived from35 community–based studies published between1990 and 2012 (references shown in Online Supplementary Document), by using the median value (0.22 episodes/child–year) and inter–quartile range (IQR) 0.11–0.51 as confidence intervals.

Although there are many possible methods to distribute the global and/or regional burden estimate among individual countries, the approach used above is our preferred solution because it is epidemiologically sound and biologically intuitive insofar as it is based on the country specific prevalence of known risk factors for pneumonia, and because it can be explained in a transparent and accessible manner. Although more complex models exist, our experience is that these sometimes result in implausibly high or low estimates for some countries, the cause of which is difficult to disentangle. This model, because of its computational simplicity and epidemiologic basis, has not suffered from this problem. The model has also been shown to distribute a known overall burden by specific countries in the absence of truly nationally representative information from many (or, in this case, from most) countries in a way which is consistent with clinical and epidemiologic knowledge.

The proportion of cases of severe pneumonia (based on the WHO definition that requires presentation of lower chest wall indrawing, and represents an indication for hospitalization) for LMIC was computed based on 9 community–based studies in LMIC that reported the proportion of severe pneumonia episodes among all pneumonia episodes (references shown in Online Supplementary Document). The median value was 11.5% (IQR 8.0–33.0%). The incidence of pneumonia in high–income countries, based on a smaller number of very large, high–quality studies (references shown in Online Supplementary Document), was also estimated using medians (and IQR): it was 0.015 e/cy in EUROA and AMROA regions; 0.030 e/cy in EURO Band 0.060 in EURO C. The mean of those values (for the whole HIC region), weighted by their under–five population size, was0.024 e/cy [52]. Approximately 26.7% (IQR 20.0–46.7%) of those episodes are estimated to progress to severe pneumonia, based on several studies from high–income countries (references shown in Online Supplementary Document). The estimates for the number of incident and severe pneumonia episodes derived in this way did not account for the use and effect of pneumococcal conjugate vaccine (PCV) and Hib vaccination coverage in 2010 at this stage of the estimation process, so the values from this step are not considered the final pneumonia burden numbers.

## Etiologic fractions of pneumonia and severe pneumonia cases

We split both the incidence and severe morbidity of childhood pneumonia by etiological agents while adjusting for the effects PCV and Hib vaccines according to country specific coverage values provided for 2010 by the UNICEF [53]. In doing so, we used the proportional contributions to all childhood pneumonia and severe childhood pneumonia from previous burden estimates on SP [43], Hib [44], RSV [45] and influenza [46] and accounted for vaccine efficacy and serotype distribution of pneumococcal disease as well as dual use of Hib and PCV where relevant. All further details are available in Online Supplementary Document.

## Country–specific estimates of the number of deaths from childhood pneumonia

This was available for 2010 from Li et al. [41]. A more recent update was made available by the UN Inter–Agency Group for Child Mortality Estimation IGME in UNICEF's 2012 report, which we term a "2010–2011" estimate [54]. Given the important focus on child mortality, and relatively minor differences compared with the Li 2010 estimates, we elected to use the 2010–11estimates for the envelopes of pneumonia deaths by country. The same decision was made in the Lancet's series [13]. The only methodological problem with this decision is a separation of Sudan and introduction of the new country – South Sudan from 2011, but we presented our results on mortality for both Sudan nations combined, and kept it within the EMRO region, although South Sudan belongs to AFRO region in the new classification [47].

## Proportional split of pneumonia deaths by etiological agent

To estimate the fraction of pneumonia deaths attributable to SP and Hib, we used the meta–analysis of the efficacy of PCV and Hib vaccines against chest X–ray confirmed pneumonia as has been described earlier (43,44), based on the assumption that the etiologic fraction of these bacteria among these particular cases approximates the etiologic fraction among the deaths. The values (33.0% for SP and 21.3% for Hib) were then adjusted by country for the use

of PCV and Hib vaccine to derive the final SP and Hib proportions [43,44,53]. Since the global disease burden estimates for flu and RSV pneumonia were not able to give point estimates and confidence intervals due to lack of data we did not attempt to go beyond the published global and regional estimates for these conditions and so did not attempt to derive national–level estimates [45,46].

## RESULTS

**Table 1** presents our estimates for 192 countries, grouped by the WHO regions: Africa (AFRO), the Americas (AMRO), Eastern Mediterranean region (EMRO), South–East Asian region (SEARO), Western Pacific region (WPRO) and European region (EURO). Several main results emerge from the presented figures. First, the population of under–five children in the world increased from 604.9 million to 633.5 million between 2000 and 2010, but the majority of the increase was observed in low– and middle–income countries (523.3 to 547.3 million), and only a smaller share in high–income countries (81.6 to 86.2 million). Holding all else constant, an increase in total child population would increase the absolute number of pneumonia cases; however, the number of cases has decreased over the past decade, because the incidence has decreased substantially. When presenting our estimates of incidence for 2000, we reported on 28 studies published between 1960 and 2000 that suggested an estimated incidence of 0.29 (0.21–0.71) episodes per child–year globally [18]. In this most recent estimate, we used 35 studies published between 1990 and 2010 with a median incidence of 0.22 (0.11–0.51). This is a notable reduction, of nearly 25%, over a period of a decade. In high–income countries we gathered more data over the past decade, and a very rough estimate of 0.05 e/cy, based on two very large, but historic studies in the USA and the UK [55,56], was refined and replaced with the data from 9 more contemporary studies, which provide a community–based incidence of 0.015 e/cy (0.012–0.020) for HIC only (WHO's "A" regions), a more plausible estimate for the modern industrial societies.

The 2000 estimate of the proportion of pneumonia episodes that are severe was 8.6% (7.0–13.0%), and was based on 6 studies, all of them from LMIC [18]. The estimate for 2010 is based on 9 studies and brings the estimate for LMIC upward, to 11.5% (8.0–33.0%). In HIC for 2000, we did not have an evidence–based estimate for the proportion of pneumonia episodes in the community that develop into severe cases. In this current analysis, we found 9 more recent studies from HIC that show a much higher estimate of the proportion – 26.7% (20.0–46.7%). However, many of them come from hospital–based studies, where more severe episodes are likely to be clustered, and a lower threshold for severity is generally applied. Still, an increasing trend in the proportion of severe episodes in LMICs seems consistent with a higher proportion expected in HICs. Nevertheless, in an effort not to overestimate the severe pneumonia burden we elected to use the proportion of pneumonia episodes developing into severe disease from the LMIC in all HIC also.

An analysis of the prevalence of exposure to the 5 main risk factors in the year 2010 in comparison to 2000 shows that the prevalence of malnutrition declined in all LMICs from 26.9% to 21.9%, low birth weight from 15.9% to 8.8%, non–exclusive breastfeeding from 64.4% to 52.6% and solid fuel use from 65.5% to 52.2% [49,50]. The exposure to all of those risk factors fell by 20–30%, which provides plausibility to the finding that our estimate of the incidence of pneumonia fell by 25% between 2000 and 2010 in LMICs. We could not perform a similar comparison with the crowding risk factor, because of the change of the definition of crowding from "5 or more" to "7 or more" residents in the same household between surveys done in 2000 and 2010.

This study also exposed rather dramatic changes in the importance of different etiological agents along the spectrum of pneumonia episode severity. At the level of all incident episodes in a community, RSV is the most common pathogen, present in about 28.8% of all episodes, followed by influenza (17.0%), while SP (adjusted for vaccine use of both Hib and PCV) is estimated to account for only 6.9% of cases and Hib (adjusted for vaccine use) in 2.8% of cases. However, at the level of severe episodes, RSV's contribution decreased to 22.6% and influenza to 7.0%, while SP rose to 18.3% and Hib to 4.1%. Bacterial etiologies become even more important in the subgroup of the children who eventually die of the disease, with the dominant causes being SP (32.7%) and Hib (15.7%). Again, both of these estimates account for Hib and PCV vaccine use in 2010.

## DISCUSSION

Although there is seemingly more evidence used in this study than there was available in the previous studies of global childhood pneumonia morbidity [1,18], the increase in evidence is only slight: 35 studies in 1990–2010 to estimate global pneumonia incidence, in comparison to 28 studies for the period 1960–2000 [18]. This also means that the studies published between 1990 and 2000 were used to produce both estimates. However, the most recent studies (those published after 2000) are consistently showing a substantially lower incidence of community–based pneumonia than was the case historically, which implies that the burden of morbidity is steadily decreasing. This also suggests that the estimates presented in this paper maybe more closely related to the situation in the year 2000 rather than 2010, because we used the information from

**Table 1.** Estimates of the number of new episodes (incidence) of community–acquired pneumonia in 2010 in children 0–4 years of age in 192 countries, shown as national–level totals (incidence, all ALRI) and by causative pathogens (SP, Hib, RSV and flu); estimates of the number of new severe episodes (according to WHO's definition) in the year 2010 that require hospitalizations, shown as national–level totals (severe episodes, all ALRI) and by causative pathogens (SP, Hib, RSV and flu); and estimates of the number of child deaths attributable to pneumonia in 2011 (mortality, all ALRI) and the proportion of deaths caused by SP and Hib

| | | | New episodes (incidence) | | | | | New severe episodes (severe morbidity) | | | | | Deaths (mortality) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | WHO Region | Population 0–4 years | All ALRI | SP | Hib | RSV | FLU | All ALRI | SP | Hib | RSV | FLU | All ALRI | SP | Hib | RSV, FLU* |
| **AFRO REGION** | | | | | | | | | | | | | | | | | |
| Algeria | AfroD | 3446548 | 470713 | 34251 | 4697 | 135754 | 80351 | 53790 | 10297 | 783 | 7315 | 2251 | 2440 | 804 | 148 | N/A |
| Angola | AfroD | 3377576 | 856794 | 62241 | 9674 | 247099 | 146255 | 97936 | 18712 | 1613 | 13293 | 4090 | 20429 | 6733 | 1398 | N/A |
| Benin | AfroD | 1506408 | 424074 | 30705 | 5895 | 122303 | 72389 | 48501 | 9231 | 983 | 6558 | 2018 | 6281 | 2070 | 522 | N/A |
| Burkina Faso | AfroD | 2955148 | 1047365 | 76085 | 11826 | 302060 | 178785 | 119719 | 22874 | 1972 | 16250 | 5000 | 17933 | 5911 | 1227 | N/A |
| Cameroon | AfroD | 3054802 | 790160 | 56858 | 14815 | 227882 | 134880 | 90462 | 17094 | 2470 | 12143 | 3736 | 13341 | 4397 | 1463 | N/A |
| Cape Verde | AfroD | 50634 | 9874 | 691 | 395 | 2848 | 1686 | 1136 | 208 | 66 | 148 | 45 | 39 | 13 | 8 | N/A |
| Chad | AfroD | 2006165 | 678297 | 48155 | 19812 | 195621 | 115785 | 77827 | 14477 | 3304 | 10285 | 3164 | 14683 | 4840 | 2390 | N/A |
| Comoros | AfroD | 122296 | 38380 | 2769 | 645 | 11069 | 6552 | 4392 | 832 | 108 | 591 | 182 | 377 | 124 | 37 | N/A |
| Equ. Guinea | AfroD | 107207 | 16341 | 1144 | 654 | 4713 | 2789 | 1879 | 344 | 109 | 244 | 75 | 402 | 132 | 85 | N/A |
| Gabon | AfroD | 185179 | 36186 | 2579 | 943 | 10436 | 6177 | 4149 | 775 | 157 | 551 | 170 | 291 | 96 | 43 | N/A |
| Gambia | AfroD | 287078 | 79805 | 2667 | 802 | 23016 | 13623 | 8746 | 802 | 134 | 1338 | 412 | 987 | 171 | 56 | N/A |
| Ghana | AfroD | 3532887 | 795448 | 57857 | 8199 | 229407 | 135783 | 90905 | 17394 | 1367 | 12357 | 3802 | 7808 | 2573 | 490 | N/A |
| Guinea | AfroD | 1657883 | 546525 | 39262 | 10948 | 157618 | 93292 | 62586 | 11804 | 1826 | 8385 | 2580 | 7689 | 2534 | 895 | N/A |
| Guin.–Bissau | AfroD | 240350 | 75199 | 5429 | 1216 | 21687 | 12836 | 8605 | 1632 | 203 | 1159 | 357 | 1592 | 525 | 152 | N/A |
| Liberia | AfroD | 680701 | 212990 | 15195 | 5418 | 61426 | 36357 | 24419 | 4568 | 903 | 3245 | 999 | 1611 | 531 | 232 | N/A |
| Madagascar | AfroD | 3305278 | 1051407 | 76189 | 13932 | 303226 | 179475 | 120231 | 22906 | 2323 | 16272 | 5007 | 8004 | 2638 | 637 | N/A |
| Mali | AfroD | 2911668 | 932894 | 67350 | 15086 | 269047 | 159245 | 106745 | 20248 | 2516 | 14384 | 4426 | 23947 | 7893 | 2292 | N/A |
| Mauritania | AfroD | 513267 | 144982 | 10415 | 2904 | 41813 | 24748 | 16603 | 3131 | 484 | 2224 | 684 | 2099 | 692 | 244 | N/A |
| Mauritius | AfroD | 84433 | 13518 | 985 | 117 | 3899 | 2307 | 1544 | 296 | 20 | 210 | 65 | 20 | 7 | 1 | N/A |
| Niger | AfroD | 3084517 | 1127652 | 81210 | 20418 | 325215 | 192490 | 129082 | 24415 | 3405 | 17344 | 5337 | 19004 | 6264 | 2018 | N/A |
| Nigeria | AfroD | 26568927 | 7339761 | 513783 | 293590 | 2116787 | 1252897 | 844072 | 154465 | 48956 | 109729 | 33763 | 121201 | 39948 | 25767 | N/A |
| S. Tome & P'e | AfroD | 23490 | 5118 | 373 | 46 | 1476 | 874 | 585 | 112 | 8 | 80 | 25 | 79 | 26 | 4 | N/A |
| Senegal | AfroD | 2081483 | 591373 | 42853 | 7836 | 170552 | 100947 | 67625 | 12883 | 1307 | 9152 | 2816 | 4612 | 1520 | 367 | N/A |
| Seychelles | AfroD | 5623 | 862 | 63 | 7 | 248 | 147 | 98 | 19 | 1 | 13 | 4 | 2 | 1 | 0 | N/A |
| Sierra Leone | AfroD | 969597 | 315676 | 22866 | 4286 | 91041 | 53886 | 36101 | 6874 | 715 | 4883 | 1503 | 7262 | 2393 | 591 | N/A |
| Togo | AfroD | 862745 | 280487 | 20292 | 4082 | 80893 | 47879 | 32083 | 6101 | 681 | 4334 | 1333 | 3321 | 1095 | 288 | N/A |
| Zimbabwe | AfroD | 1692247 | 349031 | 25271 | 4852 | 100661 | 59580 | 39918 | 7598 | 809 | 5397 | 1661 | 2461 | 811 | 205 | N/A |
| Botswana | AfroE | 225120 | 47818 | 3347 | 1913 | 13791 | 8162 | 5499 | 1006 | 319 | 715 | 220 | 159 | 52 | 34 | N/A |
| Burundi | AfroE | 1184632 | 349477 | 25440 | 3373 | 100789 | 59656 | 39933 | 7648 | 562 | 5433 | 1672 | 7259 | 2393 | 428 | N/A |
| Cen. Afr. Rep. | AfroE | 651222 | 195417 | 13981 | 4538 | 56358 | 33358 | 22394 | 4203 | 757 | 2986 | 919 | 3911 | 1289 | 520 | N/A |
| Congo | AfroE | 623244 | 168619 | 12244 | 1959 | 48630 | 28783 | 19275 | 3681 | 327 | 2615 | 805 | 2001 | 659 | 141 | N/A |
| Cote d'Ivoire | AfroE | 2969425 | 985611 | 71421 | 13060 | 284250 | 168244 | 112707 | 21472 | 2178 | 15253 | 4693 | 11003 | 3626 | 875 | N/A |
| D. Rep. Congo | AfroE | 11848026 | 3671614 | 263117 | 80589 | 1058894 | 626745 | 420631 | 79104 | 13438 | 56194 | 17291 | 86897 | 28641 | 10986 | N/A |
| Eritrea | AfroE | 861496 | 208035 | 15163 | 1802 | 59997 | 35512 | 23766 | 4559 | 301 | 3238 | 996 | 2419 | 797 | 129 | N/A |
| Ethiopia | AfroE | 11931668 | 3367561 | 240540 | 82471 | 971205 | 574843 | 386005 | 72317 | 13752 | 51372 | 15807 | 37269 | 12284 | 5196 | N/A |
| Kenya | AfroE | 6664323 | 1645189 | 119118 | 22871 | 474473 | 280834 | 188157 | 35812 | 3814 | 25440 | 7828 | 17064 | 5624 | 1419 | N/A |
| Lesotho | AfroE | 274307 | 58335 | 4224 | 811 | 16824 | 9958 | 6672 | 1270 | 135 | 902 | 278 | 607 | 200 | 50 | N/A |
| Malawi | AfroE | 2714859 | 658512 | 47877 | 7004 | 189915 | 112408 | 75261 | 14394 | 1168 | 10225 | 3146 | 6932 | 2285 | 448 | N/A |
| Mozambique | AfroE | 3876419 | 1155781 | 83373 | 19438 | 333327 | 197292 | 132266 | 25065 | 3241 | 17806 | 5479 | 13167 | 4340 | 1307 | N/A |
| Namibia | AfroE | 286374 | 63796 | 4619 | 887 | 18399 | 10890 | 7296 | 1389 | 148 | 987 | 304 | 287 | 95 | 24 | N/A |
| Rwanda | AfroE | 1830654 | 397910 | 13638 | 3991 | 114757 | 67923 | 43646 | 4100 | 666 | 6659 | 2049 | 4145 | 734 | 236 | N/A |
| South Africa | AfroE | 5041132 | 705554 | 33436 | 14342 | 203482 | 120438 | 78749 | 10052 | 2392 | 11357 | 3494 | 5156 | 1218 | 583 | N/A |
| Swaziland | AfroE | 156715 | 28802 | 2091 | 344 | 8306 | 4916 | 3293 | 629 | 57 | 446 | 137 | 471 | 155 | 34 | N/A |
| Uganda | AfroE | 6465275 | 1745727 | 126241 | 25969 | 503468 | 297996 | 199697 | 37953 | 4330 | 26961 | 8296 | 21181 | 6981 | 1876 | N/A |
| U. R. Tanzania | AfroE | 8009544 | 2151379 | 156285 | 24291 | 620458 | 367240 | 245913 | 46986 | 4051 | 33378 | 10270 | 17467 | 5757 | 1195 | N/A |
| Zambia | AfroE | 2412190 | 576056 | 41709 | 8008 | 166135 | 98333 | 65882 | 12539 | 1335 | 8908 | 2741 | 6141 | 2024 | 511 | N/A |
| **AMRO REGION** | | | | | | | | | | | | | | | | | |
| Canada | AmroA | 1884546 | 25275 | 866 | 271 | 13709 | 8032 | 6438 | 604 | 105 | 3774 | 755 | 27 | 5 | 2 | N/A |
| Cuba | AmroA | 569056 | 8208 | 598 | 79 | 4452 | 2609 | 2178 | 417 | 31 | 1140 | 228 | 63 | 21 | 4 | N/A |
| USA | AmroA | 21650217 | 313322 | 22733 | 3845 | 169946 | 99574 | 83169 | 15868 | 1489 | 43355 | 8671 | 799 | 263 | 59 | N/A |
| Antigua & B'a | AmroB | 7756 | 686 | 50 | 6 | 198 | 117 | 78 | 15 | 1 | 41 | 8 | 0 | 0 | 0 | N/A |
| Argentina | AmroB | 3385831 | 311588 | 22663 | 3212 | 89862 | 53188 | 35609 | 6814 | 536 | 18616 | 3723 | 952 | 314 | 60 | N/A |
| Bahamas | AmroB | 25507 | 2514 | 182 | 23 | 725 | 429 | 287 | 55 | 4 | 151 | 30 | 25 | 8 | 1 | N/A |
| Barbados | AmroB | 14562 | 1377 | 60 | 19 | 397 | 235 | 153 | 18 | 3 | 87 | 17 | 4 | 1 | 0 | N/A |
| Belize | AmroB | 36599 | 4795 | 349 | 46 | 1383 | 819 | 548 | 105 | 8 | 287 | 57 | 9 | 3 | 1 | N/A |
| Brazil | AmroB | 15156449 | 1497706 | 95518 | 14711 | 431938 | 255658 | 169535 | 28717 | 2453 | 91150 | 18230 | 3079 | 916 | 181 | N/A |
| Chile | AmroB | 1219437 | 88722 | 6448 | 973 | 25588 | 15145 | 10141 | 1938 | 162 | 5296 | 1059 | 145 | 48 | 10 | N/A |
| Colombia | AmroB | 4497661 | 488486 | 31421 | 6092 | 140879 | 83385 | 55372 | 9446 | 1016 | 29585 | 5917 | 1530 | 459 | 113 | N/A |
| Costa Rica | AmroB | 362979 | 37185 | 1272 | 425 | 10724 | 6348 | 4080 | 382 | 71 | 2389 | 478 | 24 | 4 | 2 | N/A |
| Dominica | AmroB | 5924 | 703 | 51 | 6 | 203 | 120 | 80 | 15 | 1 | 42 | 8 | 0 | 0 | 0 | N/A |
| Dominican R. | AmroB | 1054063 | 121820 | 8813 | 1773 | 35133 | 20795 | 13934 | 2650 | 296 | 7239 | 1448 | 587 | 193 | 51 | N/A |
| El Salvador | AmroB | 616802 | 72388 | 3616 | 829 | 20877 | 12357 | 8079 | 1087 | 138 | 4515 | 903 | 221 | 54 | 15 | N/A |
| Grenada | AmroB | 9687 | 1021 | 74 | 10 | 295 | 174 | 117 | 22 | 2 | 61 | 12 | 0 | 0 | 0 | N/A |
| Guyana | AmroB | 64818 | 7186 | 523 | 72 | 2072 | 1227 | 821 | 157 | 12 | 429 | 86 | 19 | 6 | 1 | N/A |
| Honduras | AmroB | 966002 | 184407 | 13435 | 1658 | 53183 | 31478 | 21068 | 4039 | 277 | 11036 | 2207 | 478 | 157 | 26 | N/A |
| Jamaica | AmroB | 246543 | 31065 | 2264 | 269 | 8959 | 5303 | 3549 | 681 | 45 | 1860 | 372 | 104 | 34 | 6 | N/A |
| Mexico | AmroB | 11094854 | 1110027 | 40375 | 11872 | 320132 | 189482 | 122060 | 12138 | 1980 | 71108 | 14222 | 4069 | 759 | 248 | N/A |
| Panama | AmroB | 345142 | 38834 | 2112 | 415 | 11200 | 6629 | 4354 | 635 | 69 | 2404 | 481 | 128 | 33 | 8 | N/A |
| Paraguay | AmroB | 740282 | 139661 | 10141 | 1623 | 40278 | 23840 | 15965 | 3049 | 271 | 8330 | 1666 | 368 | 121 | 26 | N/A |
| St. Kitts & N's | AmroB | 4582 | 441 | 32 | 4 | 127 | 75 | 50 | 10 | 1 | 26 | 5 | 0 | 0 | 0 | N/A |
| Saint Lucia | AmroB | 15115 | 1492 | 109 | 14 | 430 | 255 | 170 | 33 | 2 | 89 | 18 | 0 | 0 | 0 | N/A |
| St. Vinc. & G's | AmroB | 9254 | 967 | 70 | 8 | 279 | 165 | 110 | 21 | 1 | 58 | 12 | 1 | 0 | 0 | N/A |
| Suriname | AmroB | 47543 | 6578 | 477 | 85 | 1897 | 1123 | 752 | 143 | 14 | 392 | 78 | 20 | 7 | 2 | N/A |
| Trinidad & Tobago | AmroB | 95484 | 9784 | 710 | 114 | 2822 | 1670 | 1118 | 214 | 19 | 584 | 117 | 38 | 13 | 3 | N/A |
| Uruguay | AmroB | 246446 | 17570 | 647 | 188 | 5067 | 2999 | 1933 | 194 | 31 | 1125 | 225 | 53 | 10 | 3 | N/A |
| Venezuela | AmroB | 2926202 | 308502 | 22291 | 4789 | 88972 | 52661 | 35295 | 6702 | 799 | 18310 | 3662 | 927 | 305 | 85 | N/A |
| Bolivia | AmroD | 1234922 | 137114 | 9915 | 2040 | 39544 | 23405 | 15685 | 2981 | 340 | 8145 | 1629 | 1909 | 629 | 169 | N/A |

**Table 1.** (continued)

| | | | New episodes (incidence) | | | | | New severe episodes (severe morbidity) | | | | | Deaths (mortality) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | WHO Region | Population 0–4 years | All ALRI | SP | Hib | RSV | FLU | All ALRI | SP | Hib | RSV | FLU | All ALRI | SP | Hib | RSV, FLU* |
| Ecuador | AmroD | 1469919 | 163860 | 10901 | 1437 | 47257 | 27971 | 18596 | 3277 | 240 | 9934 | 1987 | 712 | 219 | 38 | N/A |
| Guatemala | AmroD | 2167408 | 481781 | 35042 | 4966 | 138946 | 82240 | 55058 | 10535 | 828 | 28785 | 5757 | 2012 | 663 | 126 | N/A |
| Haiti | AmroD | 1237203 | 345081 | 24156 | 13803 | 99521 | 58905 | 39684 | 7262 | 2302 | 19842 | 3968 | 4090 | 1348 | 870 | N/A |
| Nicaragua | AmroD | 677569 | 141434 | 10304 | 1272 | 40790 | 24143 | 16159 | 3098 | 212 | 8464 | 1693 | 503 | 166 | 28 | N/A |
| Peru | AmroD | 2909336 | 313170 | 12566 | 3545 | 90318 | 53458 | 34584 | 3778 | 591 | 19904 | 3981 | 1040 | 211 | 67 | N/A |
| **EMRO REGION** | | | | | | | | | | | | | | | | |
| Bahrain | EmroB | 93006 | 9763 | 327 | 91 | 2816 | 1667 | 1070 | 98 | 15 | 227 | 101 | 5 | 1 | 0 | N/A |
| Cyprus | EmroB | 63553 | 7253 | 528 | 70 | 2092 | 1238 | 829 | 159 | 12 | 156 | 69 | 1 | 0 | 0 | N/A |
| Iran (Isl. Rep.) | EmroB | 6149331 | 729564 | 51069 | 29183 | 210406 | 124537 | 83900 | 15354 | 4866 | 15102 | 6712 | 4168 | 1374 | 886 | N/A |
| Jordan | EmroB | 816013 | 87843 | 6400 | 790 | 25334 | 14995 | 10036 | 1924 | 132 | 1893 | 841 | 268 | 88 | 15 | N/A |
| Kuwait | EmroB | 281414 | 29357 | 994 | 284 | 8467 | 5011 | 3218 | 299 | 47 | 681 | 303 | 38 | 7 | 2 | N/A |
| Lebanon | EmroB | 321684 | 35518 | 2569 | 517 | 10243 | 6063 | 4063 | 773 | 86 | 760 | 338 | 49 | 16 | 4 | N/A |
| Libyan A. J. | EmroB | 715540 | 80748 | 5883 | 726 | 23288 | 13784 | 9225 | 1769 | 121 | 1740 | 773 | 60 | 20 | 3 | N/A |
| Oman | EmroB | 281883 | 32111 | 1074 | 300 | 9261 | 5481 | 3518 | 323 | 50 | 746 | 332 | 25 | 4 | 1 | N/A |
| Qatar | EmroB | 90524 | 9669 | 331 | 97 | 2788 | 1650 | 1061 | 100 | 16 | 224 | 100 | 4 | 1 | 0 | N/A |
| Saudi Arabia | EmroB | 3145187 | 337985 | 11445 | 3273 | 97475 | 57694 | 37052 | 3441 | 546 | 7842 | 3485 | 372 | 65 | 20 | N/A |
| Syrian A. R. | EmroB | 2493561 | 280849 | 20309 | 4178 | 80997 | 47941 | 32127 | 6106 | 697 | 6006 | 2669 | 572 | 189 | 51 | N/A |
| Tunisia | EmroB | 868231 | 99837 | 6989 | 3993 | 28793 | 17042 | 11481 | 2101 | 666 | 2067 | 919 | 209 | 69 | 44 | N/A |
| U. A. Emir. | EmroB | 420630 | 46752 | 1660 | 517 | 13483 | 7981 | 5137 | 499 | 86 | 1079 | 480 | 14 | 3 | 1 | N/A |
| Afghanistan | EmroD | 5545968 | 2040302 | 146694 | 39565 | 588423 | 348280 | 233617 | 44102 | 6598 | 43379 | 19280 | 30913 | 10189 | 3494 | N/A |
| Djibouti | EmroD | 113169 | 24926 | 1808 | 306 | 7189 | 4255 | 2850 | 544 | 51 | 535 | 238 | 446 | 147 | 33 | N/A |
| Egypt | EmroD | 9008118 | 680363 | 47625 | 27215 | 196217 | 116138 | 78242 | 14318 | 4538 | 14084 | 6259 | 4765 | 1570 | 1013 | N/A |
| Iraq | EmroD | 5188175 | 893131 | 62519 | 35725 | 257579 | 152457 | 102710 | 18796 | 5957 | 18488 | 8217 | 7568 | 2494 | 1609 | N/A |
| Morocco | EmroD | 3021924 | 385554 | 27959 | 3343 | 111194 | 65814 | 44029 | 8406 | 557 | 8316 | 3696 | 3103 | 1019 | 165 | N/A |
| Pakistan | EmroD | 21418111 | 6728235 | 487755 | 86960 | 1940423 | 1148510 | 769337 | 146640 | 14501 | 144236 | 64105 | 64853 | 21376 | 5039 | N/A |
| Somalia | EmroD | 1667479 | 650669 | 45547 | 26027 | 187653 | 111069 | 74827 | 13693 | 4340 | 13469 | 5986 | 18089 | 5962 | 3846 | N/A |
| Sudan | EmroD | 6391368 | 2061300 | 148754 | 34001 | 594479 | 351864 | 235876 | 44722 | 5670 | 43989 | 19550 | 26894 | 8864 | 3681 | N/A |
| Yemen | EmroD | 4057096 | 1150463 | 83436 | 14494 | 331793 | 196384 | 131540 | 25084 | 2417 | 24673 | 10966 | 15193 | 5008 | 1152 | N/A |
| **SEARO REGION** | | | | | | | | | | | | | | | | |
| Indonesia | SearoB | 21578876 | 3918360 | 274285 | 156734 | 1130055 | 668864 | 450611 | 82462 | 26135 | 99135 | 22531 | 19147 | 6311 | 4071 | N/A |
| Sri Lanka | SearoB | 1892699 | 433688 | 31610 | 3757 | 125076 | 74030 | 49545 | 9503 | 626 | 11425 | 2597 | 298 | 98 | 16 | N/A |
| Thailand | SearoB | 4360687 | 648021 | 45361 | 25921 | 186889 | 110617 | 74522 | 13638 | 4322 | 16395 | 3726 | 903 | 298 | 192 | N/A |
| Timor Leste | SearoB | 192839 | 67370 | 4716 | 2695 | 19429 | 11500 | 7748 | 1418 | 449 | 1704 | 387 | 489 | 161 | 104 | N/A |
| Bangladesh | SearoD | 14707333 | 4484527 | 326317 | 44752 | 1293338 | 765509 | 512461 | 98105 | 7462 | 117940 | 26805 | 18310 | 6035 | 1114 | N/A |
| Bhutan | SearoD | 70891 | 12773 | 894 | 511 | 3684 | 2180 | 1469 | 269 | 85 | 323 | 73 | 152 | 50 | 32 | N/A |
| DPR of Korea | SearoD | 1704446 | 393494 | 27545 | 15740 | 113484 | 67169 | 45252 | 8281 | 2625 | 9955 | 2263 | 1744 | 575 | 371 | N/A |
| India | SearoD | 127960004 | 35361230 | 2475286 | 1414449 | 10198179 | 6036162 | 4066541 | 744177 | 235859 | 894639 | 203327 | 388144 | 127932 | 82519 | N/A |
| Maldives | SearoD | 25984 | 4061 | 284 | 162 | 1171 | 693 | 467 | 85 | 27 | 103 | 23 | 6 | 2 | 1 | N/A |
| Myanmar | SearoD | 3956305 | 1213300 | 84931 | 48532 | 349916 | 207110 | 139530 | 25534 | 8093 | 30697 | 6976 | 9129 | 3009 | 1941 | N/A |
| Nepal | SearoD | 3506023 | 832451 | 58272 | 33298 | 240079 | 142099 | 95732 | 17519 | 5552 | 21061 | 4787 | 5501 | 1813 | 1170 | N/A |
| **WPRO REGION** | | | | | | | | | | | | | | | | |
| Australia | WproA | 1457527 | 32776 | 1204 | 385 | 17778 | 10416 | 8374 | 841 | 149 | 2724 | 1654 | 38 | 7 | 3 | N/A |
| Brunei D'lam | WproA | 37385 | 899 | 65 | 9 | 488 | 286 | 239 | 46 | 3 | 70 | 42 | 3 | 1 | 0 | N/A |
| Japan | WproA | 5430793 | 135770 | 9504 | 5431 | 73642 | 43148 | 36251 | 6634 | 2103 | 10150 | 6163 | 231 | 76 | 49 | N/A |
| New Zealand | WproA | 311974 | 7036 | 264 | 90 | 3816 | 2236 | 1800 | 184 | 35 | 583 | 354 | 31 | 6 | 2 | N/A |
| Singapore | WproA | 230550 | 5764 | 403 | 231 | 3126 | 1832 | 1539 | 282 | 89 | 431 | 262 | 9 | 3 | 2 | N/A |
| Cambodia | WproB | 1491690 | 373583 | 27150 | 4096 | 107741 | 63771 | 42699 | 8162 | 683 | 12489 | 7583 | 2101 | 693 | 140 | N/A |
| China | WproB | 81595595 | 6488544 | 454198 | 259542 | 1871296 | 1107594 | 746183 | 136551 | 43279 | 208931 | 126851 | 43089 | 14202 | 9161 | N/A |
| Cook Islands | WproB | 2096 | 210 | 15 | 2 | 61 | 36 | 24 | 5 | 0 | 7 | 4 | 0 | 0 | 0 | N/A |
| Fiji | WproB | 89552 | 14426 | 1051 | 125 | 4161 | 2463 | 1648 | 316 | 21 | 484 | 294 | 30 | 10 | 2 | N/A |
| Kiribati | WproB | 9948 | 1625 | 118 | 18 | 469 | 277 | 186 | 35 | 3 | 54 | 33 | 19 | 6 | 1 | N/A |
| Lao Peop's DR | WproB | 682861 | 212441 | 15325 | 3573 | 61268 | 36264 | 24312 | 4607 | 596 | 7049 | 4280 | 1076 | 355 | 107 | N/A |
| Malaysia | WproB | 2828151 | 285716 | 20781 | 2945 | 82400 | 48772 | 32652 | 6248 | 491 | 9559 | 5804 | 199 | 66 | 12 | N/A |
| Marshall Isl. | WproB | 5400 | 934 | 59 | 10 | 269 | 159 | 106 | 18 | 2 | 32 | 19 | 5 | 2 | 0 | N/A |
| Micronesia | WproB | 13237 | 2620 | 118 | 50 | 756 | 447 | 292 | 35 | 8 | 91 | 55 | 23 | 5 | 2 | N/A |
| Mongolia | WproB | 296799 | 60292 | 4389 | 582 | 17388 | 10292 | 6889 | 1320 | 97 | 2019 | 1226 | 332 | 109 | 20 | N/A |
| Nauru | WproB | 1025 | 97 | 7 | 1 | 28 | 16 | 11 | 2 | 0 | 3 | 2 | 1 | 0 | 0 | N/A |
| Niue | WproB | 152 | 15 | 1 | 0 | 4 | 3 | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | N/A |
| Palau | WproB | 2046 | 211 | 12 | 4 | 61 | 36 | 24 | 3 | 1 | 7 | 4 | 0 | 0 | 0 | N/A |
| Papua N. G. | WproB | 962437 | 166267 | 11905 | 3755 | 47951 | 28382 | 19051 | 3579 | 626 | 5476 | 3325 | 2038 | 672 | 264 | N/A |
| Philippines | WproB | 11254421 | 2428448 | 170059 | 96399 | 700364 | 414536 | 279254 | 51127 | 16075 | 78227 | 47495 | 8974 | 2958 | 1896 | N/A |
| R. of Korea | WproB | 2371820 | 249811 | 17487 | 9992 | 72045 | 42643 | 28728 | 5257 | 1666 | 8044 | 4884 | 56 | 18 | 12 | N/A |
| Samoa | WproB | 22338 | 3377 | 245 | 43 | 974 | 576 | 386 | 74 | 7 | 113 | 68 | 7 | 2 | 1 | N/A |
| Solomon Isl. | WproB | 79962 | 19101 | 1381 | 290 | 5509 | 3261 | 2185 | 415 | 48 | 635 | 386 | 59 | 20 | 5 | N/A |
| Tonga | WproB | 13792 | 2223 | 162 | 19 | 641 | 379 | 254 | 49 | 3 | 75 | 45 | 4 | 1 | 0 | N/A |
| Tuvalu | WproB | 1015 | 126 | 9 | 2 | 36 | 22 | 14 | 3 | 0 | 4 | 3 | 0 | 0 | 0 | N/A |
| Vanuatu | WproB | 33152 | 8344 | 584 | 334 | 2406 | 1424 | 960 | 176 | 56 | 269 | 163 | 9 | 3 | 2 | N/A |
| Viet Nam | WproB | 7185862 | 1728193 | 124101 | 35174 | 498411 | 295003 | 197920 | 37310 | 5865 | 57086 | 34660 | 3553 | 1171 | 420 | N/A |
| **EURO REGION** | | | | | | | | | | | | | | | | |
| Andorra | EuroA | 4001 | 58 | 4 | 1 | 31 | 18 | 15 | 3 | 0 | 9 | 2 | 0 | 0 | 0 | N/A |
| Austria | EuroA | 386431 | 5604 | 406 | 78 | 3040 | 1781 | 1488 | 283 | 30 | 913 | 186 | 5 | 2 | 0 | N/A |
| Belgium | EuroA | 616259 | 8882 | 647 | 80 | 4817 | 2823 | 2356 | 452 | 31 | 1456 | 296 | 7 | 2 | 0 | N/A |
| Croatia | EuroA | 389100 | 5610 | 409 | 52 | 3043 | 1783 | 1488 | 285 | 20 | 919 | 187 | 8 | 2 | 0 | N/A |
| Czech Rep. | EuroA | 547804 | 7892 | 575 | 68 | 4280 | 2508 | 2093 | 401 | 26 | 1294 | 263 | 23 | 7 | 1 | N/A |
| Denmark | EuroA | 326007 | 4413 | 168 | 55 | 2394 | 1402 | 1129 | 117 | 21 | 770 | 157 | 5 | 1 | 0 | N/A |
| Estonia | EuroA | 78229 | 1129 | 82 | 12 | 613 | 359 | 300 | 57 | 5 | 185 | 38 | 2 | 1 | 0 | N/A |
| Finland | EuroA | 299477 | 4314 | 314 | 37 | 2340 | 1371 | 1144 | 219 | 14 | 708 | 144 | 7 | 2 | 0 | N/A |
| France | EuroA | 3974436 | 53589 | 2019 | 534 | 29067 | 17031 | 13698 | 1409 | 207 | 9391 | 1910 | 61 | 12 | 3 | N/A |
| Germany | EuroA | 3466740 | 49718 | 3450 | 516 | 26967 | 15800 | 13146 | 2408 | 200 | 8192 | 1666 | 67 | 21 | 4 | N/A |
| Greece | EuroA | 586137 | 8500 | 615 | 118 | 4610 | 2701 | 2257 | 430 | 46 | 1385 | 282 | 35 | 12 | 3 | N/A |
| Hungary | EuroA | 490804 | 7071 | 515 | 61 | 3835 | 2247 | 1875 | 360 | 24 | 1160 | 236 | 27 | 9 | 1 | N/A |
| Iceland | EuroA | 23511 | 339 | 25 | 3 | 184 | 108 | 90 | 17 | 1 | 56 | 11 | 0 | 0 | 0 | N/A |
| Ireland | EuroA | 358318 | 5011 | 282 | 53 | 2718 | 1592 | 1307 | 197 | 21 | 847 | 172 | 4 | 1 | 0 | N/A |

**Table 1.** (continued)

| | | New episodes (incidence) | | | | | | New severe episodes (severe morbidity) | | | | | Deaths (mortality) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | WHO Region | Population 0–4 years | All ALRI | SP | Hib | RSV | FLU | All ALRI | SP | Hib | RSV | FLU | All ALRI | SP | Hib | RSV, FLU* |
| Israel | EuroA | 735243 | 10618 | 772 | 113 | 5759 | 3375 | 2818 | 539 | 44 | 1737 | 353 | 13 | 4 | 1 | N/A |
| Italy | EuroA | 2901653 | 41871 | 3047 | 418 | 22711 | 13307 | 11109 | 2127 | 162 | 6856 | 1395 | 30 | 10 | 2 | N/A |
| Luxembourg | EuroA | 28783 | 389 | 15 | 4 | 211 | 124 | 100 | 11 | 1 | 68 | 14 | 0 | 0 | 0 | N/A |
| Malta | EuroA | 19130 | 278 | 20 | 4 | 151 | 88 | 74 | 14 | 2 | 45 | 9 | 0 | 0 | 0 | N/A |
| Monaco | EuroA | 2001 | 29 | 2 | 0 | 16 | 9 | 8 | 1 | 0 | 5 | 1 | 0 | 0 | 0 | N/A |
| Netherlands | EuroA | 934218 | 12528 | 435 | 126 | 6795 | 3981 | 3192 | 303 | 49 | 2208 | 449 | 18 | 3 | 1 | N/A |
| Norway | EuroA | 303047 | 4085 | 150 | 45 | 2216 | 1298 | 1044 | 105 | 17 | 716 | 146 | 3 | 1 | 0 | N/A |
| Poland | EuroA | 1933388 | 27852 | 2030 | 241 | 15107 | 8851 | 7388 | 1417 | 93 | 4568 | 929 | 126 | 41 | 7 | N/A |
| Portugal | EuroA | 516604 | 7448 | 542 | 69 | 4040 | 2367 | 1976 | 379 | 27 | 1221 | 248 | 3 | 1 | 0 | N/A |
| San Marino | EuroA | 1401 | 20 | 1 | 0 | 11 | 6 | 5 | 1 | 0 | 3 | 1 | 0 | 0 | 0 | N/A |
| Serbia & Montenegro | EuroA | 604144 | 8747 | 634 | 110 | 4744 | 2780 | 2322 | 443 | 43 | 1428 | 290 | 30 | 10 | 2 | N/A |
| Slovakia | EuroA | 275895 | 3688 | 123 | 34 | 2000 | 1172 | 938 | 86 | 13 | 652 | 133 | 35 | 6 | 2 | N/A |
| Slovenia | EuroA | 99368 | 1433 | 104 | 14 | 777 | 455 | 380 | 73 | 5 | 235 | 48 | 2 | 1 | 0 | N/A |
| Spain | EuroA | 2521375 | 36353 | 2647 | 339 | 19718 | 11553 | 9644 | 1848 | 131 | 5958 | 1212 | 50 | 16 | 3 | N/A |
| Sweden | EuroA | 557426 | 7682 | 382 | 72 | 4167 | 2441 | 1989 | 266 | 28 | 1317 | 268 | 10 | 2 | 1 | N/A |
| Switzerland | EuroA | 376228 | 5431 | 395 | 56 | 2946 | 1726 | 1441 | 276 | 22 | 889 | 181 | 3 | 1 | 0 | N/A |
| UK | EuroA | 3765820 | 50844 | 1913 | 560 | 27578 | 16158 | 13000 | 1335 | 217 | 8898 | 1810 | 165 | 32 | 10 | N/A |
| Albania | EuroB | 207681 | 6230 | 436 | 249 | 3379 | 1980 | 1664 | 304 | 96 | 981 | 200 | 66 | 22 | 14 | N/A |
| Bosnia & Herzegovina | EuroB | 164958 | 4784 | 346 | 67 | 2595 | 1520 | 1270 | 242 | 26 | 780 | 159 | 24 | 8 | 2 | N/A |
| Bulgaria | EuroB | 373095 | 10245 | 470 | 122 | 5557 | 3256 | 2643 | 328 | 47 | 1763 | 359 | 219 | 50 | 15 | N/A |
| Georgia | EuroB | 256459 | 7488 | 539 | 143 | 4061 | 2380 | 1990 | 376 | 55 | 1212 | 247 | 108 | 36 | 12 | N/A |
| Romania | EuroB | 1079244 | 32377 | 2266 | 1295 | 17561 | 10290 | 8645 | 1582 | 501 | 5100 | 1037 | 807 | 266 | 172 | N/A |
| FYR Macedonia | EuroB | 111863 | 3236 | 235 | 39 | 1755 | 1029 | 859 | 164 | 15 | 529 | 108 | 10 | 3 | 1 | N/A |
| Turkey | EuroB | 6412702 | 172393 | 6203 | 1724 | 93506 | 54786 | 43984 | 4330 | 667 | 30306 | 6164 | 2212 | 408 | 126 | N/A |
| Armenia | EuroB | 226376 | 6661 | 475 | 167 | 3613 | 2117 | 1773 | 332 | 65 | 1070 | 218 | 80 | 26 | 11 | N/A |
| Azerbaijan | EuroB | 795163 | 23855 | 1670 | 954 | 12939 | 7581 | 6369 | 1166 | 369 | 3758 | 764 | 1448 | 477 | 308 | N/A |
| Kyrgyzstan | EuroB | 595111 | 17168 | 1250 | 166 | 9312 | 5456 | 4555 | 872 | 64 | 2812 | 572 | 599 | 197 | 35 | N/A |
| Tajikistan | EuroB | 870519 | 25144 | 1828 | 267 | 13638 | 7991 | 6672 | 1276 | 104 | 4114 | 837 | 2097 | 691 | 136 | N/A |
| Turkmenistan | EuroB | 505844 | 14823 | 1062 | 325 | 8040 | 4711 | 3943 | 741 | 126 | 2391 | 486 | 824 | 271 | 104 | N/A |
| Uzbekistan | EuroB | 2737750 | 82133 | 5749 | 3285 | 44549 | 26102 | 21929 | 4013 | 1272 | 12938 | 2632 | 4970 | 1638 | 1057 | N/A |
| Belarus | EuroC | 514996 | 30900 | 2163 | 1236 | 16760 | 9820 | 8250 | 1510 | 479 | 4868 | 990 | 51 | 17 | 11 | N/A |
| Kazakhstan | EuroC | 1640953 | 94676 | 6892 | 914 | 51352 | 30088 | 25117 | 4811 | 354 | 15510 | 3155 | 1408 | 464 | 83 | N/A |
| Latvia | EuroC | 115275 | 6673 | 484 | 82 | 3619 | 2121 | 1771 | 338 | 32 | 1090 | 222 | 19 | 6 | 1 | N/A |
| Lithuania | EuroC | 166177 | 9592 | 698 | 96 | 5203 | 3048 | 2545 | 487 | 37 | 1571 | 319 | 19 | 6 | 1 | N/A |
| R. of Moldova | EuroC | 214693 | 12557 | 902 | 256 | 6811 | 3991 | 3339 | 629 | 99 | 2029 | 413 | 161 | 53 | 19 | N/A |
| Russian Federation | EuroC | 8117113 | 487027 | 34092 | 19481 | 264163 | 154777 | 130036 | 23797 | 7542 | 76721 | 15604 | 1618 | 533 | 344 | N/A |
| Ukraine | EuroC | 2376293 | 139669 | 9980 | 3376 | 75756 | 44387 | 37167 | 6966 | 1307 | 22460 | 4568 | 629 | 207 | 87 | N/A |

ALRI – acute lower respiratory infection, SP – *Streptococcus pneumoniae*, Hib – *Haemophilus influenzae* type B, RSV – respiratory syncytial virus, FLU – influenza virus

*For viral etiologies, N/A indicates that estimates are not available at the national level at this point, due to very little available information and high degree of uncertainty of regional and global estimates.

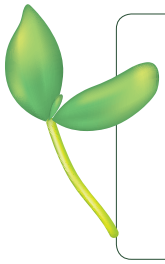
the previous two decades in the context of scarcity of information, and the true morbidity figures for 2010 are likely to be even smaller, ie, less than 0.20 e/cy. In addition, the decreasing trend is quite consistent with apparent improvements in risk factor prevalence, as recorded by DHS and MICS [49,50].

With more evidence, the proportion of pneumonia cases that are severe has been revised upward. For HIC, most of these estimates were relevant to children hospitalized for pneumonia, thus clustering the most severe cases, while most studies in LMICs are community–based and encompass a full spectrum of severity. Still, it appears that the increase in the proportion of severe episodes in the LMICs is a valid trend, given the high proportion in HICs (which may reflect increased proportion of parents seeking care and lower threshold for hospitalization). This finding may seem paradoxical (ie, that the proportion of pneumonia that is severe in nature is higher in high income settings that LMIC) and may be explained by a propensity to hospitalize children in HIC or by a faster reduction in pneumonia incidence at the community level than in the incidence of severe pneumonia episodes. We could speculate that improved social, economic and lifestyle conditions in many LMICs over the past decade have a rather major effect on pneumonia incidence in the whole population, while the cases that progress into severe episodes are still clustering in the areas with persistent poverty which are not really enjoying the benefits of economic growth, so it is more difficult to reduce them. If this is true, then the proportional contribution of severe episodes to all pneumonia episodes in the community is set to continue increasing over time, although both the cases of pneumonia in the community and severe cases are being reduced – but the former is being reduced at a faster pace than the latter.

It is reassuring that the etiological estimates for SP, Hib, RSV and influenza, which were based on entirely different data sets from those that were used for the estimates of pneumonia incidence, severe morbidity and mortality, and which were also conducted independently of each other, are all "fitting" into the envelopes of pneumonia incidence, severe morbidity and pneumonia deaths at the global, regional and (for SP and Hib) also at the national level [37–46]. At the level of pneumonia incidence, there is likely a multitude of etiological causes that contribute to pneumo-

nia in the community. Therefore, at the global level, the four major pathogens combined explain about 55% of all episodes, according to our computations, but this grows to considerably more among pneumonia deaths [43–46]. The modeling effort does not reveal whether the unattributed fractions are likely from these four pathogens or from other pathogens. As an example, at the level of severe episodes, it appears that the four pathogens explain nearly 95% of all episodes in Europe and 83% in the Americas, but only 48% in Eastern Mediterranean region and as little as 39% in sub–Saharan Africa. A large ongoing project funded by The Gates Foundation – "The Pneumonia Etiology Research for Child Health (PERCH)" study – will try to explain etiology of childhood pneumonia better at the global level [25]. It is a 7–site study in LMICs, coordinated by Johns Hopkins University, to determine the etiology, or causes, of pneumonia, and the first results are expected in the latter part of 2014 [25].

All burden of disease estimates must cope with the issue of uncertainty in the data and the estimates. All the estimates of childhood pneumonia at either global, regional or (especially) national levels are inherently uncertain, for the many reasons mentioned in the beginning of this paper. The evidence to population models remains limited, and the case definitions used across studies are not all the same, yet the estimates are rather robust. What makes them plausible, if not certain, is that they are internally consistent: mutually independent cause–specific etiology estimates "fit" into the "envelopes" of total cases, severe cases and deaths; in addition, case–fatality rates between incident cases and deaths, and severe episodes and deaths, based on our model, resemble those observed in real data. This is all reassuring, but it also needs to be noted that the estimates of uncertainty (presented in Online Supplementary Document) are still probably (substantially) under–estimated. This is because each and every parameter derived from a previous parameter (eg, proportion of all acute lower respiratory infection (ALRI) cases that are SP) has its own uncertainty, as do the estimates of vaccine effectiveness, risk factor odds ratios, rates of vaccine coverage, and all other parameters in the model. We typically expressed only uncertainty related to each specific parameter, without adding the uncertainty of all the previous parameters from which the new estimate has been derived. This makes the whole table in the Online Supplementary Document seem more precise than it actually may be, given that the uncertainties are really large, and only the consistency between different estimates in the much bigger picture is what gives it some credibility with the current amount of evidence. CHERG aims to continue identifying new sources of published and unpublished good quality data and updating these estimates regularly with this new information and so increase the quality of its estimates towards the Millennium Development Goal 4 target in 2015 and well beyond, until preventable childhood diseases are adequately controlled and responded to everywhere in the world [57,58].



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PAPERS

# Diarrhea as a risk factor for acute lower respiratory tract infections among young children in low income settings

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**Background** Diarrhea and acute lower respiratory tract infections (ALRI) are leading causes of morbidity and mortality among children under 5 years of age. We sought to quantify the correlation of diarrhea and respiratory infections within an individual child and to determine if infection with one illness increases the risk of infection with the other during the same time period.

**Methods** We quantified the likelihood of an ALRI and a diarrhea episode occurring during the same week compared to the likelihood of each occurring independently in two cohorts of children under 3 years of age using a bivariate probit regression model. We also quantified the likelihood of an ALRI episode conditioned on a child's diarrhea history and the likelihood of a diarrhea episode conditioned on a child's ALRI history using Cox Proportional Hazard models.

**Results** In Indian and Nepali children, diarrhea and ALRI occurred simultaneously more than chance alone. Incidence of ALRI increased in both cohorts as the number of days with diarrhea in the prior 28 days increased; the greatest incident rate ratio was reported among children with 20 or more days of diarrhea (1.02, 95% confidence interval (CI) 1.01 – 1.03 in Nepal and 1.07, 95% CI 1.05 – 1.09 in South India). Incidence of diarrhea was affected differently by ALRI prevalence depending on the season.

**Conclusions** Diarrhea may be a direct risk factor for ALRI among children under 3 years of age. The risk of comorbidity increases as disease severity increases, providing additional rationale for prompt community case–management of both diarrhea and pneumonia.

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Pneumonia and diarrhea are the leading causes of death among children under 5 years of age around the world [1]. In low– and middle–income countries children under 5 years of age experience multiple episodes of diarrhea each year and 1.4 episodes of pneumonia before their fifth birthday [2]. These infectious diseases disproportionately cause severe morbidity and mortality among children living in high–risk populations typically characterized by poverty and inadequate health care.

There has long been speculation that some children may be more susceptible to simultaneous infections (ie, comorbidity) or may experience sequential infections because of compromised immune function and mal-

nutrition. Although biologically plausible and clinically observable, there is little evidence quantifying the prevalence of common infectious disease comorbidities among children <3 years of age. Several studies have looked for the co–occurrence of diarrhea and pneumonia and have found that these two diseases occur together at a rate that is greater than that expected by chance [3-6].

We sought to quantify the correlation of diarrhea and respiratory infections within an individual child and determine if infection with one illness increases the risk of infection with the other during the same time period. By using cohort data, we are able to differentiate between overlapping infections and sequential infections and quantify the role of disease severity on each relationship.

## METHODS

### Selection of data sets

The analysis presented here was part of a wider portfolio of comorbidity analyses designed to quantify the risk relationships of overlapping infections, subsequent illnesses and mortality (not presented here). In this light we conducted a systematic literature review to identify studies with prospective morbidity and mortality surveillance among children under 5 years of age. We searched PubMed, Scopus, and Google Scholar for published studies between 1980 and 2010 using key words: diarrhea, pneumonia, acute lower respiratory tract infection (ALRI), morbidity and mortality. We excluded all studies that were not conducted among representative populations and had morbidity surveillance for less than 12 months. Included studies were required to have at least bi–weekly household morbidity surveillance to collect daily morbidity reports for all signs and symptoms of diarrhea and respiratory infections. We also contacted numerous investigators as part of the Child Health Epidemiology Reference Group (CHERG) (www.cherg.org) network of investigators by email and phone in an effort to identify ideal data sets.

We identified two studies that enrolled children under the age of 3 years for routine diarrhea surveillance in low– or middle–income countries. We identified one study from rural Sarlahi District in Southern Nepal (NNIPS–4 trial) that was designed as a cluster–randomized trial assessing the efficacy of preventive zinc and/or iron supplementation on morbidity and mortality [7]. All children from 1–23 months of age living in the study area were asked to participate in the main trial. Detailed morbidity data were ascertained during home visits weekly on a subset of infants from each treatment group for 12 months after enrollment.

We identified one study from South India that was designed as an individually randomized placebo-controlled trial (VASIN) assessing the efficacy of vitamin A supplementation for newborn infants [8]. Newborns were enrolled at birth and followed every two weeks until 6 months of age. Daily morbidity data were collected at each interview. For our analyses, we included only infants 1 month of age and older.

### Simultaneous correlation of ALRI and diarrhea episodes

We sought to quantify the likelihood of an ALRI and a diarrhea episode occurring during the same week compared to the likelihood of each occurring independently between two cohorts of children under 3 years of age. Daily morbidity records were summarized for each calendar week of morbidity surveillance, such that each week was classified as having no illnesses, a diarrhea episode, an ALRI episode, or both. Complete episode definitions are described in **Table 1**. Due to data limitations, we used the episode definitions as determined by the initial study investigators. We analyzed the weeks with both disease events occurring using a bivariate probit regression model. The bivariate probit analysis models both the individual prevalence of each outcome and the correlation between two simultaneous outcomes while assuming a latent normal variable [9]. The correlation within week is modeled explicitly with latent normality, while the correlation between observation weeks

**Table 1.** Study definitions for diarrhea and respiratory morbidities

| Disease | Nepal | South India |
|---|---|---|
| Diarrhea | ≥4 loose watery stools/d, with episodes separated by ≥3 symptom–free days | ≥4 loose watery stools/d, episodes separated by ≥3 symptom–free days |
| Persistent diarrhea | Diarrhea for ≥14 d | Diarrhea for ≥14 d |
| Dysentery | Blood or mucus in the stool, with ≥3 symptom–free days separating episodes | Blood or mucus in the stool, with >3 symptom–free days separating episodes |
| ALRI | Fever, cough, or difficulty breathing, with all 3 symptoms on ≥1 d during the episode with ≥7 d between episodes.<br>Respiratory rates available from sub–study to define fast breathing:<br>≥60 breaths/min if <2 mo old;<br>≥50 breaths/min if 2–11 mo of age; and<br>≥40 breaths/min ≥12 mo | Below definitions of severity with episodes separated by ≥3 symptom–free days:<br>ALRI–1: cough with fever on ≥1 d<br>ALRI–2: difficulty breathing with fever on ≥1 d<br>ALRI–3: cough and difficulty breathing with fever on ≥1 d |

ALRI – acute lower respiratory tract infection, mo – month, d – day

for the same child is accounted for in the standard errors with a robust covariance estimate. Comorbidity is quantified by the correlation of an episode of ALRI and diarrhea occurring during the same week. Given this, the correlation could range from –1, indicating an extreme inverse or protective relationship, to 1, which would indicate perfect co–occurrence of both illnesses. A value of zero would indicate that the co–occurrence of diarrhea and ALRI is by chance alone.

For the NNIPS study data, we modeled the prevalence of ALRI and diarrhea by calendar month, age in four categories (1–5, 6–11, 12–23, and 24–35 months), sex and mid–upper arm circumference. For the VASIN data set, we controlled for calendar month and sex; we did not control for age given that age was between 1–5 months.

## Is recent morbidity predictive of ALRI or diarrhea incidence rates?

We quantified the likelihood of an ALRI episode conditioned on a child's diarrhea history using daily morbidity data from the two cohorts of children. We used daily morbidity data to define the presence of an ALRI episode for each day the child was enrolled in the study such that on each day a child was either positive or negative for ALRI. We then calculated the number of days the child had an episode of diarrhea in the 28 days prior to the index day. For any day with missing data we assumed the child did not experience diarrhea, unless there was no history of diarrhea available for any day in the last 28 days in which case the day was dropped from the analysis. We then used the Prentice–Williams–Peterson model that extends Cox proportional hazards regression to recurring events to estimate the incidence rate of ALRI conditional on the number of days of diarrhea in the previous 28 days [6,10,11]. We chose calendar time as the scale for this model in order to control for seasonal variation in the rates of respiratory infection, assuming the main effect of one additional day of diarrhea in the past four weeks proportional to the rate of ALRI, and that this effect would remain the same over time. In order to best summarize the relationship between recent diarrhea and incident ALRI, several functions of the number of recent diarrhea days were considered. We organized the number of days with each illness into categories and thus approximately linear relationships were observed in each study (**Figure 1**). In addition, the individual ALRI rate was used to group children for analysis, where incidence is estimated for each group and effects are estimated across groups. This stratification compares the number of illness days for children with a similar number of episodes. To address the potential for common risk factors of diarrhea and ALRI, we included age, sex and mid upper arm circumference (MUAC) where available for each child as covariates in this model. We initially included the proportion of time–spent ill for each child, but due to colinearity this violated basic model assumptions. For graphical purposes, we calculated an average monthly incidence rate, by calendar month for each additional day of diarrhea. To illustrate the risk relationship we plotted 4 risk relationships from the results of this model with a linear effect of recent diarrhea on ALRI incidence: 1) no diarrhea in previous 28 days; 2) 5 days of diarrhea; 3) 10 days of diarrhea and 4) 20 days of diarrhea.

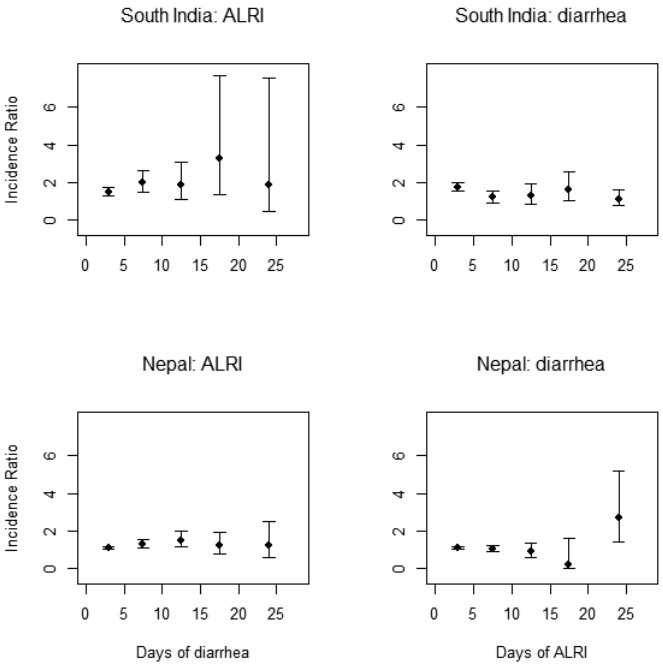



**Figure 1.** In the models for acute lower respiratory tract infection (ALRI) incidence, estimated incidence ratios for categorized diarrhea in the past 28 days, and in the models for diarrhea incidence, estimated incidence ratios for categorized history of ALRI in past 28 days.

Similarly, we estimated the likelihood of a diarrhea episode conditioned on a child's history of ALRI. We used the same episode definitions for ALRI and diarrhea as described above. Using the daily data to define each index day as positive/negative for diarrhea, we then calculated the number of days of ALRI in the previous four weeks. For any day without a morbidity record, we assumed no ALRI (as also described above). We then modeled the incidence rate of diarrhea conditional on the number of days of ALRI in the last 28 days. We assumed that this ratio remains constant over time. As we described above we calculated the average monthly incidence rate by calendar month and plotted four risk relationships for different levels of recent ALRI rates as described above.

# RESULTS

## Simultaneous correlation of ALRI and diarrhea episodes

Among 4865 Nepali children, caregivers reported 6.7% of weeks with an episode of diarrhea and 3.2% of weeks with ALRI symptoms. In this population diarrhea and ALRI were also commonly reported as simultaneous comorbidities in 0.4% of weeks. Analysis with the bivariate probit regression model showed that diarrhea and ALRI have a small positive correlation and occurred together more than chance alone (0.15, 95% confidence interval (CI) 0.13 – 0.17) (**Table 2**). The effect was more pronounced among episodes of ALRI with elevated respiratory rates. Statistical adjustment with seasonality and child level covariates (age, sex, MUAC) did not change the positive correlation (**Table 2**).

Among 11 115 South Indian infants, caregivers reported 3.9% of weeks with an episode of diarrhea and 9.5% of weeks with ALRI symptoms classified as ALRI–1, 2.0% of weeks with ALRI symptoms classified as ALRI–2, and 1.6% of ALRI symptoms classified as ALRI–3. In this population of young infants, 0.6% of weeks were classified as having diarrhea and ALRI comorbidity symptoms. The bivariate probit regression model showed that diarrhea and ALRI symptoms (of any ALRI definition) occur together more than chance alone with the strongest association being between diarrhea and ALRI as defined by difficulty breathing and a fever (ALRI–2), with an estimated correlation of 0.19 (95% CI 0.16 – 0.23) (**Table 2**). There were no differences observed between the unadjusted correlation and the adjusted correlation (**Table 2**).

## Diarrhea and/or ALRI as a risk factor for subsequent morbidities

We first calculated the incidence of ALRI by prior 28–day diarrhea history using the Prentice–Williams–Peterson Proportional Hazards model among Nepali children. These children reported an overall incidence rate of 1.4 episodes defined by reported signs or symptoms of ALRI per child year of observation. The predicted incidence rate increased as the number of days with diarrhea in the 28 days prior increased with the highest ALRI incidence rates predicted for children who reported 20 or more days of diarrhea in the preceding 28 days. The incidence ratio was modeled as a linear function of the number of days with diarrhea in the past 28, where the incidence ratio for one additional day of diarrhea was estimated at 1.02 (95% CI 1.01– 1.03) (**Figure 2**). This relationship was constant across seasons.

We used the same methodology to assess the reverse relationship, ie, diarrhea incidence as a function of the signs and symptoms of ALRI in the preceding 28 days. Unlike

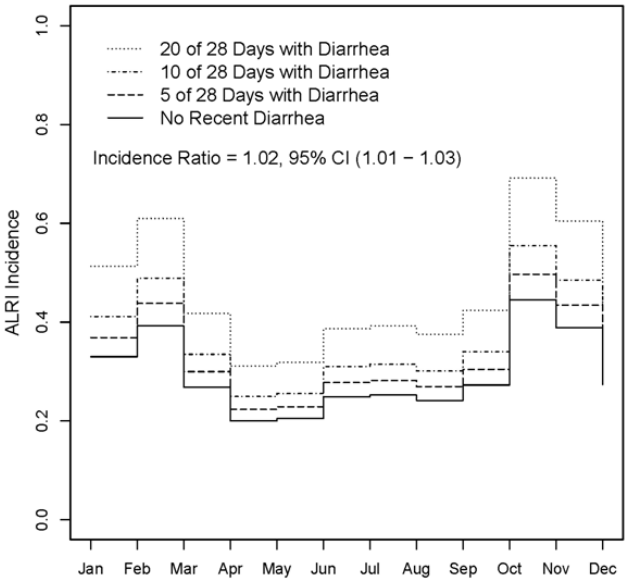



**Figure 2.** Estimated acute lower respiratory tract infection (ALRI) incidence by month and history of diarrhea in past 28 days for Nepali children.

**Table 2.** Correlation between weekly ALRI and diarrhea episodes as observed in the bivariate probit regression models among Nepali children and South Indian infants

| | Estimate | Lower Limit | Upper Limit | Standard Error |
|---|---|---|---|---|
| **Nepali Children** | | | | |
| Unadjusted: | 0.153 | 0.132 | 0.174 | 0.011 |
| ALRI & diarrhea | | | | |
| ALRI & diarrhea with elevated respiratory rate | 0.296 | 0.149 | 0.431 | 0.072 |
| Adjusted:* | | | | |
| ALRI & diarrhea | 0.146 | 0.125 | 0.167 | 0.011 |
| ALRI & diarrhea with elevated respiratory rate | 0.250 | 0.092 | 0.395 | 0.078 |
| **South Indian Infants** | | | | |
| Unadjusted: | | | | |
| ALRI–1& diarrhea | 0.150 | 0.130 | 0.171 | 0.011 |
| ALRI–2 & diarrhea | 0.190 | 0.163 | 0.227 | 0.016 |
| ALRI–3 & diarrhea | 0.170 | 0.134 | 0.203 | 0.017 |
| Adjusted:† | | | | |
| ALRI–1& diarrhea | 0.150 | 0.128 | 0.169 | 0.011 |
| ALRI–2 & diarrhea | 0.190 | 0.161 | 0.225 | 0.016 |
| ALRI–3 & diarrhea | 0.170 | 0.132 | 0.201 | 0.018 |

ALRI – acute lower respiratory tract infection, ALRI–1: cough with fever on ≥1 day, ALRI–2: difficulty breathing with fever on ≥1 day, ALRI–3: cough and difficulty breathing with fever on ≥1 day

*Adjusted for calendar time, age, sex, and mean upper arm circumference (MUAC).

†Adjusted for calendar time and sex.

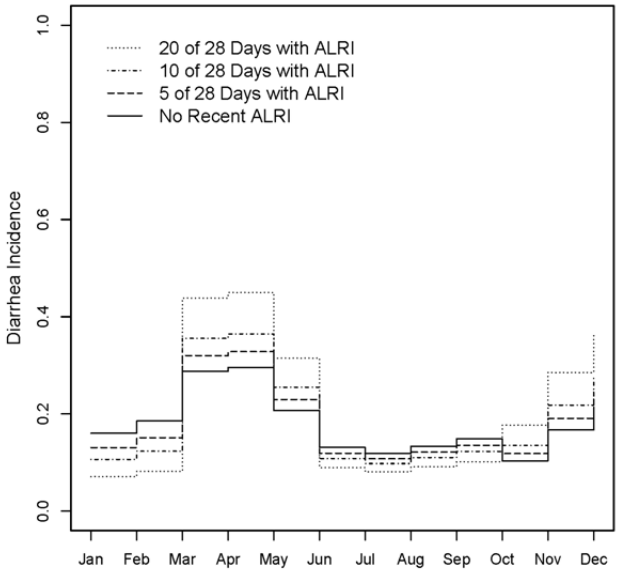



**Figure 3.** Estimated diarrhea incidence by month and history of acute lower respiratory tract infection (ALRI) in past 28 days for Nepali children.

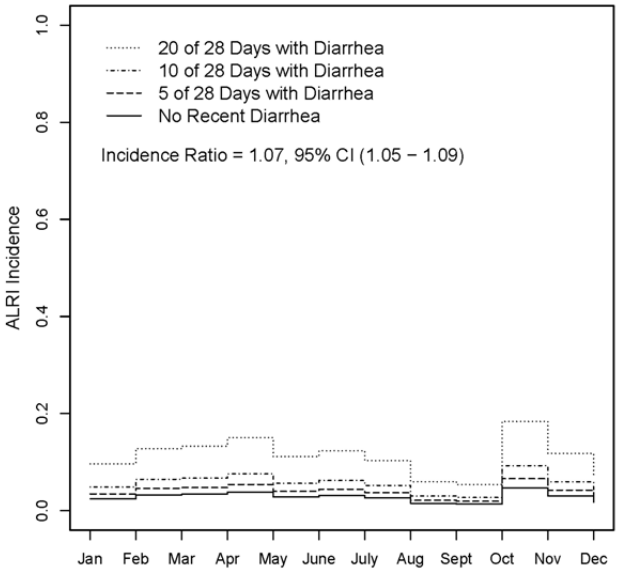



**Figure 4.** Estimated acute lower respiratory tract infection (ALRI) incidence by time and history of diarrhea in past 28 days among South Indian infants.

the above analysis, the diarrhea incidence rate was affected differently by prevalence of ALRI symptoms depending on the time of year. The overall estimated linear effect of recent diarrhea days on ALRI incidence was negligible and not statistically significant, however, a Wald test for an interaction of effect with season was significant at alpha = 0.05. In the summer (March – May), diarrhea incidence rate was higher for those with ALRI symptoms (1.02, 95% CI 1.00 – 1.04), however, in other months, diarrhea incidence did not vary significantly by prevalence of prior ALRI symptoms (**Figure 3**).

We then calculated the incidence of ALRI (the most severe of the 3 ALRI definitions presented earlier) by 28–day diarrhea history among South Indian infants as was done in the Nepali children. Among these infants, the overall incidence rate of ALRI per child–year of observation was 0.3 episodes/child year. For these young babies an increase in the number of days with diarrhea was predictive of increased ALRI incidence with the highest ALRI incidence rates predicted for babies with 20 or more days of diarrhea in the past 28 days. For one additional day of diarrhea, the estimated incidence ratio was 1.07 (95% CI 1.05 – 1.09) (**Figure 4**). ALRI history was also more predictive of an increased rate of diarrhea with the highest diarrhea incidence rates predicted among infants with more than 20 days of ALRI in the preceding 28 days, but only in the summer (March–May, incidence ratio 1.03, 95% CI 1.01 – 1.06) and the monsoon season (June–September, incidence ratio 1.02, 95% CI 1.00 – 1.03) (**Figure 5**). Like the analysis using the Nepali data, the test for interaction between number of recent ALRI days and season was significant at alpha = 0.05, so the model with a constant effect of recent ALRI days on diarrhea incidence over time is not shown.

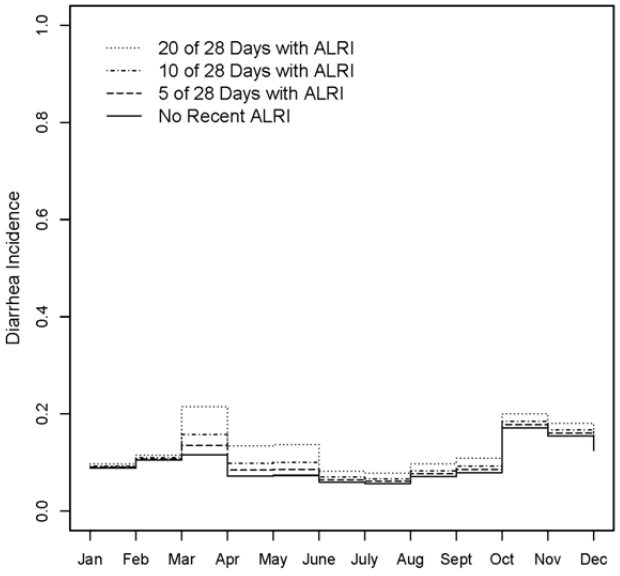



**Figure 5.** Estimated diarrhea incidence by time and history of acute lower respiratory tract infection (ALRI) in past 28 days among South Indian infants

## DISCUSSION

We conducted two analyses to determine the relationship of ALRI and diarrhea among young children in Nepal and South India. In these low–income settings, we assessed the presence of diarrhea and ALRI alone as well as the likeli-

hood of both occurring during the same week. In both populations, we found that ALRI and diarrhea present as simultaneous comorbidities more than would be expected by chance alone. This correlation increased in strength as severity of infection increased. In the second analysis we found that children in both countries who experienced more days of diarrhea had increased risk for subsequent ALRI episodes. However, the risk of diarrhea contingent upon prevalence of ALRI was only observed in some seasons.

Fenn et al [12] conducted a similar analysis using the bivariate probit regression model to quantify the simultaneous comorbidity among a cohort of children in rural Ghana. They too observed simultaneous comorbidity with diarrhea and ALRI occurring more than chance alone, and were also able to quantify this for varying degrees of disease severity. The correlation of combined infection increased as disease severity increased. In the Nepal and South Indian data sets, we were not able to differentiate episodes into disease severity beyond the 3 categories presented in the South Indian cohort. Future comorbidity analyses will benefit from detailed morbidity data such that correlations between multiple categories of disease severity can be assessed.

We conducted our analysis utilizing two large cohort studies that enabled us to assess the longitudinal daily prevalence of both diarrhea and ALRI. This permitted us to analyze ALRI as a risk factor for diarrhea and vice versa. Schmidt et al [6] conducted a similar analysis among Ghanaian and Brazilian children and found diarrhea prevalence to be a risk factor for ALRI among Ghanaian children, but not among Brazilian children. They postulated that this difference could be attributed to large differences in socioeconomic and epidemiologic conditions between the two populations; as could also be observed by the 10–fold difference in mortality rates between the two study populations. Coles et al [13] also observed diarrhea to be a risk factor for community–acquired alveolar pneumonia in Bedouin children in Israel. In our analysis of Nepali and South Indian children, we found the risk relationship to be much stronger for diarrhea as a risk factor for ALRI as compared to ALRI as a risk factor for diarrhea, which was significant only in certain seasons or among the South Indian infants.

There are several possible mechanisms or possible explanations for simultaneous and sequential infections. While it is possible that the signs and symptoms of diarrhea can mimic those of pneumonia, eg, severe diarrhea and dehydration can lead to metabolic acidosis and result in rapid, shallow breathing, it is an unlikely explanation for our findings [14]. First, diarrhea of that severity was rare in the studies analyzed and second, this would not explain the relationship with the respiratory illness following diarrhea, rather than being simultaneous with it; simultaneous infections were only recorded in less than 1% of observed weeks. It is well known that diarrhea can often lead to nutritional setbacks and hence the start of a cycle of illness, growth failure, and subsequent developmental delays [15]. These analyses suggest that the same cycle may not be observed given an episode of ALRI and thus the longer–term effects on growth, development, and immune function may differ between diarrhea and ALRI. One possible explanation for this effect is the loss of zinc during diarrhea, increasing the occurrence of zinc deficiency which in turn increases the risk of both ALRI and diarrhea [16]. Beyond the biological explanations for comorbidity, it is also possible that children with one infection are at greater risk for subsequent infections introduced at the point of care–seeking by increasing contact with children carrying other pathogens. It has also been observed that children living in the poorest houses are more exposed to infection as a result of lack of access to prevention and treatment interventions and thus sick children tend to live and play around other sick children exacerbating the cycle of infection [17].

Our analyses had a number of strengths. The study populations are both representative of rural low–income settings in South Asia, but provide two unique perspectives with regard to possible variation of comorbidity by age. The weekly prevalence of disease differed between the two populations, as did the relationship between diarrhea and ALRI comorbidity. This might be explained simply by anticipating variation when conducting analyses between two unique populations or might be more strongly related to the differences in age. However, our goal was not to compare one population to the other, rather to look for consistencies in the directionality and magnitude of the effects. Because these cohort studies used active community–based survey teams to gather morbidity data, we are able to look at the natural history of disease and determine how each individual illness affects the child's health in the subsequent weeks and months.

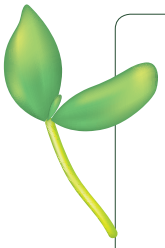
Our analyses also have a number of limitations. As with any secondary analysis, we were limited to the data that had already been collected several years ago and thus not able to perform sub–group analyses by disease severity, or to control for common risk factors of ALRI and diarrhea beyond what was originally collected. Specifically, counted respiratory rates as well as X–ray confirmation of pneumonia for all children would have improved the case definition of ALRI and led to better associations of the relationship between diarrhea and pneumonia, in lieu of more general ALRI episodes. In addition, because these studies primarily gathered all information on the child's signs and symptoms using household interviews with 1–2 week recall periods, the sensitivity and specificity of defining an episode has limitations. A caregiver might forget to recall minor episodes from several days prior, an episode could

escalate in the days immediately following the interview and not be captured well during the next interview, or caregivers may forget several signs and symptoms over time. While daily surveillance of signs and symptoms would permit such measurements as counted respiratory rates and temperature, these frequent visits can also alter the natural history of disease by increasing the likelihood of care–seeking through early case detection and active referral reducing the ability to find a relationship. In addition, differences in recall period (7–day recall in Nepal vs 14–day recall in South Asia) may have also introduced bias.

Where daily data were missing, we assumed no disease for either diarrhea or ALRI. This may be underestimating incidence and days ill for both diseases, but given higher incidence rates of diarrhea, this would be more pronounced for diarrhea. Though this is a limitation, the effect would be an underestimation of the relationship between diarrhea and ALRI.

Lastly, in our analysis we only considered the short–term associations between diarrhea and ALRI. Further analyses of the longer–term associations that should include detailed anthropometric data in addition to disease surveillance are needed. We still do not fully understand the relationship of multiple infections either occurring together or in sequence during a very short time period, the results of these analyses suggest that comorbidity is a quantifiable problem and should be further investigated to better understand the full consequences of disease for both diarrhea and ALRI.

In the analysis here and in past reports [6,13], diarrhea has been shown to be an important risk factor for ALRI and it might be hypothesized that it may also be an important risk factor for ALRI/pneumonia cause–specific mortality, but further studies are needed to make the leap from morbidity to mortality. When calculating burden of disease, episodes and deaths from diarrhea and pneumonia are typically not considered as risk factors or contributing causes which may underestimate the true disease burden of these infectious diseases. This is becoming especially apparent for diarrhea for which the cycle of infection and undernutrition has long been recognized, but not fully quantified [15]. These new analyses further suggest the role of diarrhea as a direct risk factor for ALRI and highlight the importance of additional research to more fully understand the immunologic and biochemical mechanisms of this relationship.



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**Ethical approval:** Not required.

**Authorship declaration:** CLFW and JP conceptualized the analysis. CLFW wrote the first draft of the manuscript. JP conducted the analysis. JK and JMT collected the data and contributed to the analytic plan and final manuscript preparation. REB contributed to the analytic plan, interpretation and final manuscript preparation.

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**Electronic supplementary material:**
The online version of this article contains supplementary material.

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# Treatment of diarrhea in young children: Results from surveys on the perception and use of oral rehydration solutions, antibiotics, and other therapies in India and Kenya

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**Background** Diarrheal disease is a leading cause of morbidity and mortality among children under five. Although oral rehydration solution (ORS) has tremendous therapeutic benefits, coverage of and demand for this product have remained low in many developing countries. This study surveyed caregivers and health care providers in India and Kenya to gather information about perceptions and use of various diarrhea treatments, assess reasons for low ORS use, and identify opportunities for expanding ORS use.

**Methods** The project team conducted two rounds of semi–structured, quantitative surveys with more than 2000 caregivers in India and Kenya in 2012. A complementary survey covered more than 500 pharmacy staff and health care workers in both countries. In Kenya, the team also surveyed rural pharmacies to gather pricing and sales data.

**Results** Although caregivers generally had very positive perceptions of ORS, they typically ranked antibiotics ahead of ORS as the strongest medicine for diarrhea (in India 62% ranked antibiotics first and 23% ranked ORS first, n = 404; in Kenya results were 55% and 29%, n = 401). Many caregivers had misconceptions about the purpose and effectiveness of various treatments. For example, most caregivers who gave ORS at last episode expected it to stop their child's diarrhea (65% in India, n = 190; 73% in Kenya, n = 154). There were noteworthy differences between India and Kenya in the selection and sourcing of treatments. Much of the money spent by families during the last episode of diarrhea was for inappropriate treatments. This was especially true in India, where rural households typically spent US$ 2.29 (median for the 79% of rural households that paid for health care services or treatments, n = 199) with most of this going to pay fees of private health workers and/or for antibiotics.

**Conclusions** Caregivers' primary treatment goal is to stop diarrhea, and many believe that antibiotics or ORS will accomplish this goal. Inappropriate treatment – and especially overuse of antibiotics – is common. Satisfaction with ORS is high, but dosing is a challenge for caregivers. The results provide valuable insight into treatment behaviors and suggest significant opportunities to enhance use of ORS in developing countries.

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Diarrheal disease is a leading cause of morbidity and mortality among children under five and accounts for approximately 800 000 deaths annually in this age group, mostly in developing countries [1].More than 580 million moderate to severe episodes of diarrhea occur annually in children under five, most of which result in some dehydration [2]. Since the late 1970s, oral rehydration solution (ORS) has been the most commonly recommended treatment for dehydration caused by diarrhea. More than 90% of all diarrhea deaths could potentially be avoided with universal coverage of ORS [3].

Despite the overwhelming burden of illness and the tremendous therapeutic benefits of ORS, coverage and demand in many developing countries has remained stubbornly low, with fewer than 40% of children under five in developing countries receiving ORS for the treatment of diarrhea. Coverage is particularly low among the most vulnerable: poor children and those in rural areas [4]. More specifically, in the context of ORS use or nonuse, there is a substantial "know–do gap" among caregivers. Although demographic and health survey data from many countries indicate that most mothers or caregivers are familiar with ORS as a diarrhea treatment there is little correlation between knowledge and actual use of the product [5].

The reasons for low use of ORS are a long–standing source of speculation. Some suggest that mothers do not use ORS because it does not treat the symptoms, it tastes bad, or because it does not look like a "real medicine" [6]. Others attribute low ORS use to the availability of alternative treatment products, particularly antibiotics [7]. A better understanding of the reasons for use or nonuse of ORS and other interventions could help inform public health and commercial efforts to promote or market ORS more effectively, and in turn increase coverage.

This paper presents the results of a series of surveys administered to more than 2000 caregivers and more than500 providers in India and Kenya. It examines their approaches to diarrhea treatment and the sequence of interventions used, reasons for use or nonuse of ORS and other interventions, expectations and preferences of interventions, costs associated with diarrhea treatment, and dosing. India and Kenya were selected as both are often settings of interest. While the same surveys were conducted in parallel in both countries, the study was not structured as a comparative exercise per se. These results should prove very helpful for efforts to increase ORS coverage.

## METHODS

The project team conducted two rounds of semi–structured quantitative surveys with caregivers in India and Kenya, using the same surveys and methods in both countries. It was not a comparative study and minor local variations in the surveys and methods may have occurred. The first round (R1) occurred in April and May 2012 and the second (R2) in August 2012. A complementary, semi–structured quantitative survey with pharmacy staff and health care workers was conducted in May and June 2012. Selected methods and results from the provider survey are also included in this report. In Kenya, the team also conducted a rural pharmacy survey in June and July2012 to gather pricing and sales data.

### Selection and description of participants

Quota–sampling was used to recruit two groups of caregivers: 1) those who had ever used ORS and 2) those who were aware of ORS but had never used it (hereafter referred to as 'ever–users' and 'never–users'). To be eligible for either group, the caregiver must have had a child under five who had an episode of diarrhea, of any sort, within two months prior to the interview. Quotas were used to recruit approximately equal numbers of urban and rural respondents. Finally, quotas for states/provinces were used, with the sample distributed in proportion to the reported incidence of ORS usage [8,9] and spread across 18 (Kenya) to 27 (India) sampling points. States/provinces were selected to achieve appropriate representation of major socio–cultural regions, higher– and lower–coverage of ORS, areas of greater commercial relevance, and areas of more acute public health need. Within states/provinces, sampling points were purposively selected, and interviewers used systematic random sampling to identify respondents during recruitment. **Table 1** presents a profile of respondents.

A similar, quota–based approach was used for the survey of pharmacy staff and health care workers, and this relied on purposive sampling (Online Supplementary Document, table s1). Purposive selection was also used for the Kenya rural pharmacy survey, which covered 49 pharmacies in Coast, Eastern, and Nyanza provinces.

### Technical information

The R1 and R2 surveys with caregivers emphasized experience with the latest episode of diarrhea among children under five years (ie, the single most recent diarrhea episode among this age–group in the household). Topics included diarrhea duration, treatments used and sequence/timeframes of administration, and caregivers' expectations of each treatment used – "what did you think [the treatment] would do for your child?" The R1 survey (~60 minutes) also probed for treatment source, and the R2 survey (~45 minutes) asked about treatment spending and dosing of ORS and sugar–salt solution (SSS) at the last episode of diarrhea. The spending and dosing questions merit elaboration. For each treatment they had used, caregivers were asked whether they had paid for it, and if so, about how

**Table 1.** Characteristics of the responders in two rounds of caregivers surveys (R1 and R2)

| Characteristics | India | | Kenya | |
|---|---|---|---|---|
| | R1 survey | R2 survey | R1 survey | R2 survey |
| All respondents | 609 | 404 | 600 | 401 |
| Ever–users of ORS | 320 | 209 | 320 | 210 |
| Never–users, but aware of ORS | 289 | 195 | 280 | 191 |
| Urban | 50% | 50% | 50% | 50% |
| Rural | 50% | 50% | 50% | 50% |
| Age 18–24 | 34% | 35% | 38% | NR |
| Age 25–34 | 59% | 62% | 48% | NR |
| Age 35+ | 6% | 4% | 14% | NR |
| Age distribution of children 6–59 mo:* | | | | |
| 6–11 mo | 28% | 29% | 31% | 29% |
| 12–23 mo | 29% | 27% | 30% | 38% |
| 24–35 mo | 30% | 32% | 31% | 27% |
| 36–59 mo | 46% | 43% | 46% | 47% |
| Hospitalized at last diarrhea episode | 20 (3%) | NR | 12 (2%) | NR |
| Socioeconomic level:† | | | | |
| A, B (India, urban only; Kenya, all) | 37% | 35% | – | 5% |
| C1, C2 (India, urban; Kenya, all [C1/C2]) | 9% | 6% | 48% (13/35) | 57% (15/42) |
| D, E (India, urban; Kenya, all) | 4% | 9% | 52% | 38% |
| R1, R2 (India, rural) | 10% | 13% | – | – |
| R3, R4 (India, rural) | 40% | 37% | – | – |
| Region: | | | – | – |
| Uttar Pradesh (India) / Nairobi (Kenya) | 124 | 90 | 97 | 65 |
| Tamil Nadu (India) / Coast (Kenya) | 74 | 43 | 106 | 71 |
| Andhra Pradesh (India) / Nyanza (Kenya) | 83 | 51 | 153 | 102 |
| Maharashtra (India) / Rift Valley (Kenya) | 127 | 93 | 244 | 163 |
| Jharkand | 31 | 22 | – | – |
| West Bengal | 102 | 69 | – | – |
| Madya Pradesh | 68 | 36 | – | – |

R1 – survey 1, R2 – survey 2, NR – not recorded

* Percentages are per age group; addition across age groups gives values over 100 percent due to the presence of multiple children in some households. Socioeconomic levels: A is highest and E lowest; in India, R1 denotes the highest rural grade and R4 the lowest.

†Socioeconomic levels: A is highest and E lowest; in India, R1 denotes the highest rural grade and R4 the lowest. Socioeconomic classification was based on the standard systems used for commercial market research in the respective countries; in India, as described in "Harmonization of demographics: a manual for research agencies and users" (Market Research Society of India, Mumbai, 2011) [10]. In Kenya, the categories as initially defined by the British National Readership Survey (and often used in market research globally) were used with adapted criteria in common use among members of the Marketing and Social Research Association of Kenya.

much (except for SSS and other home remedies). Then caregivers were asked if they "had paid anything else, such as doctor's fees, consultation fees, or clinic fees." Interviewers recorded any items mentioned and the spending corresponding to each. The survey did not cover other costs such as for transport or lost work time. Peak dosing estimates were calculated using conservative assumptions to err on the side of over–estimating the amounts given. Caregivers were asked to think about the day on which their child's diarrhea was "particularly bad" and were then asked how many times they gave ORS on that day and approximately how much ORS they gave each time. Frequencies of administration were recorded as ranges (eg, 1 to 2 times, 3 to 4 times) and then rounded up in the analysis (to 2 and 4 times, respectively, for example). Responses were typically expressed and recorded in terms of either "a few spoonfuls" or simple fractions of "a cup', and high assumptions were then taken for each (eg, 25 mL for "a few spoonfuls" and 250 mL for 1 cup).

Other topics covered by the quantitative surveys with caregivers included demographics; awareness and ever–use of treatments (ORS sachets, SSS, other home remedies, antibiotics, antimotility drugs, zinc syrups/tablets, and, in India, pre–mixed ORS available in ready–to–drink packs; a localized photo–illustration card was used to assist in recall of treatment types); perceptions of ORS, using positive–negative statement pairs; and preferred speed of action and willingness to pay for a treatment for diarrhea, generally. The R1 survey also covered general attitudes and awareness in relation to treatment of diarrhea in young children, preferred product presentations, and preferred ORS pack sizes. The R2 survey included forced–rankings for the 3 main treatments (as identified at R1) on each of 4 separate parameters: effectiveness, strength, ease of use, and value.

The provider survey (~40 minutes) was tailored to the various types of health care workers and pharmacy staff interviewed. Topics included estimates of what caregivers would pay for a treatment, providers' views of various treatments' roles and effectiveness, profit–related influences, and caregiver expectations.

Development of the survey instruments benefited from a careful process of formative research and pretesting. Formative research was conducted with all respondent types

in multiple regions of each country. Open–ended, in–depth individual interviews and group discussions were used to explore the range of attitudes and behaviors, including perceptions of treatments and possible product features. In both countries, a small team of 2–3 experienced local researchers led all of the interviews/discussions and performed the analysis. These researchers and the core team met in a workshop to bridge from the formative research to design of the surveys and instruments. The R1 survey instrument went through two rounds of pretesting with a few dozen respondents in each country. Special attention was given to the questions relating to treatment behaviors at last episode. The R2 instrument was lightly pretested; many of its main questions were carried over from the R1 survey, initial results of which were utilized to inform design of the R2 instrument.

### Statistical methods

The closed–ended data from both the R1 and R2 surveys were analyzed in a similar manner. The initial, base analysis included an examination of data at a total respondent level as well as by key groups such as ever–users vs never–users, urban vs rural. Additional subgroups of interest were identified during the analysis to elicit areas of differentiation or drivers of behavior. An extensive series of subgroup analyses were performed. For example, the possibility of differences in treatment behaviors between various socioeconomic and demographic subgroups was carefully explored. All salient findings are presented as results. Certain forms of questioning also called for specific types of analyses. For example, because a broad set of detailed questions was asked about the last diarrhea episode, subsequent analysis required aggregation across the episode at an individual respondent level to build patterns of product usage. Although elements of the initial base analysis were designed a priori, much of the analysis was conducted post hoc after the complete results of each survey were ready for analysis.

Open–ended data from the R1 and R2 surveys were analyzed through a similar procedure. The process began with review of verbatim responses for each question. Key common themes were identified for each question, as well as factors associated with each theme. This represented a code frame. Each verbatim response was then analyzed and assigned to its appropriate code.

## RESULTS

### Caregiver perceptions and expectations influencing treatment decisions

When caregivers were asked about their expectations for treatment, "Stop the diarrhea" was the most frequent response (**Table 2**). When they were asked "What is the longest period of time that would be acceptable to you from first giving your child something for diarrhea until the child's bowel movements return to normal?", the mean response (±standard deviation) was 1.7 ± 1.2 days in India and 1.6 ± 1.1 in Kenya (Online Supplementary Document, table s2).

**Table 3** shows how caregivers ranked treatments based on 4 criteria: most effective at treating the cause of diarrhea, strongest medicine for diarrhea, easiest to get children to take, and best use of money to treat diarrhea. Antibiotics tended to outrank ORS in both countries, although ORS ranked appreciably better in Kenya than in India. More caregivers ranked antibiotics first on effectiveness and strength than ranked ORS first on these attributes, although the mar-

**Table 2.** Expectations (% respondents) of main treatments, when used to treat at last episode of diarrhea

| Principal expectations of treatments (%) | India | | | Kenya | | |
|---|---|---|---|---|---|---|
| | Antibiotics (n=238) | ORS (n=190) | SSS (n=270) | Antibiotics (n=189) | ORS (n=154) | SSS (n=155) |
| Stop the diarrhea | 91 | 65 | 41 | 70 | 73 | 59 |
| Replace fluids lost due to diarrhea | 11 | 62 | 73 | 13 | 51 | 39 |
| Improve child's energy level | 43 | 59 | 31 | 17 | 36 | 14 |
| Improve child's health | 51 | 38 | 32 | 8 | 8 | 6 |
| Reduce frequency of bowel movements | 37 | 33 | 26 | 10 | 8 | 14 |
| Reduce vomiting or fever† | 28 | 23 | 24 | – | – | – |
| Help treat diarrhea faster | 24 | 15 | 6 | 12 | 5 | 6 |
| Reduce pains† | – | – | – | 18 | 6 | 15 |
| Kills all bacteria or germs† | – | – | – | 32 | 5 | 7 |

ORS – oral rehydration solution, SSS – sugar–salt solution

*R2 survey. This exercise was used in open–ended format in the R1 survey, and in closed–ended format at R2. Analysis of R1 results led to the pre–codes used at R2; the option of an open–ended 'other' response was included, and respondents were not prompted at R1 or R2.

†Indicates expectations which were not mentioned for any main treatment by at least 8% in one of the countries (India or Kenya), and have been truncated with "–".

**Table 3.** Ranking of main treatments (% rating as the 1st choice)

| Treatment | All respondents | | Used antibiotics and ORS both* | | Used antibiotics but not ORS* | | Used ORS but not antibiotics* | |
|---|---|---|---|---|---|---|---|---|
| | India (n=404) | Kenya (n=401) | India (n=131) | Kenya (n=79) | India (n=112) | Kenya (n=154) | India (n=58) | Kenya (n=58) |
| **Most effective at treating the cause of diarrhea:** | | | | | | | | |
| Antibiotics | 52 | 45 | 59 | 46 | 86 | 48 | 9 | 22 |
| ORS | 25 | 35 | 37 | 53 | – | 14 | 78 | 74 |
| SSS | 23 | 20 | 5 | 1 | 14 | 39 | 14 | 3 |
| **Strongest medicine for diarrhea:** | | | | | | | | |
| Antibiotics | 62 | 55 | 67 | 58 | 88 | 57 | 12 | 34 |
| ORS | 23 | 29 | 31 | 41 | – | 10 | 78 | 62 |
| SSS | 15 | 15 | 2 | 1 | 12 | 32 | 10 | 3 |
| **Easiest to get children to take:** | | | | | | | | |
| Antibiotics | 22 | 35 | 15 | 28 | 44 | 40 | 3 | 17 |
| ORS | 31 | 39 | 60 | 61 | – | 10 | 67 | 81 |
| SSS | 47 | 26 | 2 | 11 | 56 | 49 | 29 | 2 |
| **Best use of money to treat diarrhea:** | | | | | | | | |
| Antibiotics | 73 | 50 | 63 | 41 | 100 | 73 | 14 | 24 |
| ORS | 27 | 50 | 37 | 59 | – | 28 | 86 | 76 |

ORS – oral rehydration solution, SSS - sugar–salt solution
*Used at last episode of diarrhea.

gin in favor of antibiotics was narrower in Kenya. Kenyan caregivers were split equally as to whether antibiotics or ORS represent the best use of money, but Indian caregivers favored antibiotics over ORS by 3 to 1 on value. Among caregivers who used both antibiotics and ORS for the last episode, the differences in results between India and Kenya are even more pronounced (**Table 3**). In Kenya, most ranked ORS ahead of antibiotics on both effectiveness and value, while ranking antibiotics ahead on strength by a margin of 3 to 2. In India, by contrast, antibiotics were ranked much further ahead of ORS on these attributes.

Among caregivers who used antibiotics and *not* ORS during the last episode, a group that could be expected to most favor antibiotics, results from India were heavily in favor of antibiotics. The same group in Kenya, however, was less enthusiastic about antibiotics and ranked them similarly on effectiveness and strength as did Kenyan caregivers who had used both antibiotics and ORS. Also, many ranked SSS first (**Table 3**).

When caregivers were asked about their expectations for specific treatments during the most recent episode 'Stop the diarrhea' was the most common expectation for both antibiotics and ORS in both countries (**Table 2**). Antibiotics scored much higher than ORS on "stop the diarrhea" in India (91% vs. 65% across all users; and 95% vs. 53% in the two lower, rural socioeconomic grades), and they scored on par with ORS in Kenya (70% vs.73%, **Table 2**). Expectations results for the two lower, rural socioeconomic grades in India correspond to grades R3 and R4 combined (antibiotics, n=238; ORS, n=190; SSS, n=270). Caregivers' expectations for treatments were broadly consistent with the reasons they gave for their ranking of the main treatments (Online Supplementary Document, table s3).

Although ORS outscored SSS on most benefits in both countries, SSS did score higher on "replace fluids" response in India, where caregivers in the two lower rural socioeconomic grades had especially high expectations for ORS (73%) and SSS (84%) to replace fluids. In Kenya, fluid replacement was mentioned less often for both ORS (51%) and SSS (39%) as compared to India (62% and 73%, respectively; **Table 2**). More than half of health care workers and pharmacy staff in Kenya and more than one–third in India agreed with the statement "mothers do not really understand that ORS rehydrates the child" (Online Supplementary Document, table s4).

**Table 4** focuses on caregiver perceptions of ORS, as reflected in agreement or disagreement with various statements about ORS. Overall, perceptions of ORS were quite positive among both ever– and never–users. Most caregivers in both countries indicated that they believed ORS is a medicine and that it stops diarrhea. This was true for both ever– and never–users.

There was concern among caregivers in both countries, however, that ORS was too much liquid for a child to take, that it needs to be given too often, and that there is often liquid leftover that goes to waste. The first two of these concerns were mentioned more frequently in India (82% and 73%) than in Kenya (30% and 25%). In Kenya, about one–third of caregivers indicated dissatisfaction with the taste of ORS and the difficulty of getting a child to drink it. These issues were not as important among caregivers in India (**Table 4**). In R1 interviews, 97% of caregivers in India (n = 609) and 92% in Kenya (n = 190) agreed with the statement that "children with diarrhea need more water and liquids".

**Table 4.** Caregiver perceptions (% response) of ORS, on Positive [negative] paired statements*

| Perception | India | | | | Kenya | | | |
|---|---|---|---|---|---|---|---|---|
| | Ever–users of ORS (n = 320) | | Never–users but aware of ORS (n = 289) | | Ever–users of ORS (n = 320) | | Never–users but aware of ORS (n = 280) | |
| | Positive | Negative | Positive | Negative | Positive | Negative | Positive | Negative |
| Helps [does not help] replace fluid/water and minerals lost due to diarrhea | 98 | 1 | 91 | 2 | 96 | 2 | 74 | 5 |
| Easy [difficult] to obtain such products | 97 | 2 | 91 | 4 | 88 | 11 | 74 | 12 |
| Restores [does not] the child's energy and appetite | 97 | 2 | 85 | 3 | 89 | 6 | 62 | 9 |
| ORS increases [does not] the child's energy | 97 | 1 | 87 | 1 | 90 | 7 | 61 | 8 |
| Instructions on how to prepare it are clear [unclear] | 97 | 1 | 86 | 4 | 95 | 3 | 64 | 6 |
| I am confident [not confident] that the water I use to make ORS is clean | 94 | 4 | 90 | 5 | 90 | 7 | 57 | 18 |
| Rehydrates [does not rehydrate] the child | 94 | 2 | 91 | 2 | 96 | 3 | 76 | 4 |
| Easy [difficult] to prepare | 92 | 6 | 91 | 2 | 94 | 5 | 75 | 8 |
| Reduces [does not reduce] the child's bowel movements | 92 | 4 | 82 | 6 | 85 | 12 | 60 | 16 |
| I feel [do not feel] confident that I know how to prepare ORS properly | 92 | 7 | 83 | 6 | 93 | 6 | 54 | 24 |
| Stops the diarrhea [does not stop the diarrhea] | 92 | 6 | 79 | 4 | 80 | 17 | 57 | 18 |
| Relieves stomach pains the child may have [does not relieve] | 91 | 2 | 76 | 3 | 67 | 19 | 41 | 18 |
| Does not take a lot of time and effort to prepare [takes a lot of time and effort] | 88 | 11 | 83 | 13 | 89 | 10 | 64 | 13 |
| Easy [difficult] to get the child to drink it | 88 | 11 | 68 | 16 | 66 | 32 | 42 | 30 |
| Does not usually [usually] cause children to vomit | 84 | 10 | 59 | 15 | 71 | 25 | 46 | 18 |
| Not an expensive treatment [expensive treatment] | 83 | 14 | 78 | 16 | 88 | 7 | 74 | 8 |
| Easy [difficult] to obtain clean water to make it | 83 | 16 | 71 | 26 | 75 | 22 | 68 | 21 |
| Is [not] a medicine | 78 | 20 | 68 | 27 | 92 | 6 | 77 | 9 |
| Nice pleasant taste [not nice and unpleasant taste] | 75 | 17 | 66 | 10 | 57 | 38 | 31 | 35 |
| Rarely [often] have liquid left over which is wasted | 60 | 36 | 47 | 31 | 54 | 42 | 31 | 32 |
| The frequency of giving these products to the child is acceptable [you need to give these products to the child too often] | 38 | 59 | 20 | 64 | 65 | 32 | 49 | 23 |
| Not too much liquid for a young child to take [too much liquid for a child to take] | 15 | 82 | 14 | 73 | 67 | 30 | 45 | 25 |

ORS – oral rehydration solution

*Positive – chose ORS–positive statement; Negative– chose ORS–negative statement. "Don't know" responses are not shown, but are equal to 100% less the sum of the positive and negative response percentages; DK responses were more common among never–users.

## Treatment choice, timing, dosing, and sourcing

Antibiotics were used to treat about half of episodes in both countries, regardless of ORS use (**Table 5**). Most ORS ever–users also reported use of ORS during the last episode (India 91%, Kenya 75%). Use of SSS or other home remedies was fairly common among both ORS ever–users and never–users and was higher in India than in Kenya. Reported use of other treatments, such as zinc and antimotility drugs, was low.

Use of only one treatment (ie, monotherapy) was more common in Kenya than in India (**Table 5**). In Kenya, 36% of ORS ever–users and 65% of never–users used monotherapy (most often antibiotics). In India, by contrast, only 6% of ORS ever–users and 24% of never–users used monotherapy, reflecting higher reported use of ORS, SSS, and other home remedies. In India there were also notable differences in treatment usage between socioeconomic grades, with more antibiotic use among lower, rural grades and greater use of SSS and other home remedies among higher grades (Online Supplementary Document, table s5).

The duration of the last episode was typically 3 to 4 days in both countries (Online Supplementary Document, table s6). When given, SSS or other home remedies were typically started on day 1 and given for a median of 3 days in India and 2 days in Kenya (Online Supplementary Document, table s6). When ORS was given, it was typically started on day 2 and given for 3 days. When antibiotics were used, they were typically started on day 2 and given for 3 days (India) or 4 days (Kenya). Most Indian caregivers (75%) took action on day 1 by adjusting the child's diet or starting a treatment. Forty percent of Kenyan caregivers,

**Table 5.** Treatments given at last episode of diarrhea*

| Treatment | India | | Kenya | |
|---|---|---|---|---|
| | Ever–users of ORS | Never–users but aware of ORS | Ever–users of ORS | Never–users but aware of ORS |
| All treatments given, as % (n=episodes treated): | n=524 | n=464 | n=494 | n=363 |
| Antibiotics | 59 | 54 | 48 | 56 |
| ORS | 91 | – | 75 | – |
| SSS | 58 | 62 | 31 | 44 |
| Other home remedy | 27 | 31 | 9 | 14 |
| Antimotilities | 3 | 3 | 10 | 11 |
| Zinc | 12 | 8 | 9 | 6 |
| Monotherapy only, as % of episodes treated | 6 | 24 | 36 | 65 |
| Monotherapy only (n=episodes so treated) | n=49 | n=196 | n=178 | n=238 |
| Antibiotics as % of monotherapies | 16 | 39 | 23 | 47 |
| ORS as % of monotherapies | 58 | – | 52 | – |
| SSS as % of monotherapies | 16 | 42 | 14 | 30 |

ORS – oral rehydration solution, SSS - sugar–salt solution

*Combined results from R1 and R2 surveys, weighted equally.

however, took a wait–and–see approach, typically for one full day.

Caregivers who gave ORS typically used a relatively low amount on the day of peak use and believed it was the most they could give their child in one day. In both countries, two thirds of those using ORS with children 6 to 24 months old (primarily 12 to 24 months old) gave less than 500 mL per day at peak, typically giving 250 mL in Kenya and 125 mL in India (median values; **Table 6**). Among caregivers in both countries who used ORS with children 24 to 60 months old, the majority gave less than 1 L per day at peak. In Kenya, these caregivers typically gave 250 mL, and in India 375 mL (medians). When SSS was used, peak dosing levels generally followed the same pattern as for ORS. Among caregivers in both countries who used ORS, at least 73% said the amount they gave per day at peak was the maximum amount they could give their child each day. Notably, caregivers in both India and Kenya who reported giving more ORS than the thresholds applied at the analysis stage (500 mL or 1 L, per age group) were also more likely to indicate it was the maximum amount they could give their child on one day (**Table 6**).

In India, private facilities were the primary source of both ORS (80%) and antibiotics (80%) (Online Supplementary Document, table s7). In Kenya, by contrast, public facilities clearly played a much larger role as sources of ORS (67%) and antibiotics (48%), though a quarter of responses about sources of antibiotics in Kenya could not be categorized.

**Table 6.** Dosing at last episode of diarrhea, ORS and SSS

| Dosing | India | | | | Kenya | | | |
|---|---|---|---|---|---|---|---|---|
| **ORS:*** | | | | | | | | |
| Age treated at last diarrhea episode: range | 6 mo to <2 y (n=61) | | 2–5 y (n=96) | | 6 mo to <2 y (n=42) | | 2–5 y (n=56) | |
| ORS given on day of peak use (mL) | <500 | ≥500 | <1000 | ≥1000 | <500 | ≥500 | <1000 | ≥1000 |
| Percentage | 67% | 33% | 82% | 18% | 64% | 36% | 91% | 9% |
| Median (IQR) amount ORS given, day of peak use | 125 mL (150) | 750 mL (250) | 375 mL (375) | 1125 mL (500) | 250 mL (150) | 500 mL (375) | 250 mL (275) | 1000 mL (500) |
| Caregivers who felt this was the maximum amount they would be able to give their child in one day | 85% | 95% | 73% | 100% | 78% | 87% | 75% | 80% |
| **SSS:*** | | | | | | | | |
| Age treated at last diarrhea episode: range | 6 mo. to <2 y (n=78) | | 2–5 y (n=135) | | 6 mo. to <2 y (n=48) | | 2–5 y (n=56) | |
| SSS given on day of peak use (mL) | <500 | ≥500 | <1000 | ≥1000 | <500 | ≥500 | <1000 | ≥1000 |
| Percentage | 78% | 22% | 95% | 5% | 73% | 27% | 98% | 2% |
| Median (IQR) amount SSS given (mL), day of peak use | 250 (125) | 500 (0) | 375 (250) | 1000 (0) | 125 (150) | 625 (375) | 125 (150) | 1000 (0) |

ORS – oral rehydration solution, SSS – sugar–salt solution, mo – month, y – year

*R2 survey. Regarding the n values in this table: For the dosing analysis, only data from households with one child aged 6–59 mo were used, to allow for sub–analysis by the two age groups shown; although households with more than one child aged 6–59 mo were also included in the surveys, and the number and ages of all such children was recorded per household (reflected in the age distribution data presented in Table 1), record was not made of which specific child had suffered the most recent episode of diarrhea. *In this range, most were aged 1 year to <2 years.

Most caregivers in both countries who used ORS or antibiotics reported doing so on a provider's recommendation. In India, recommendations figured more prominently with use of antibiotics (95%) than with use of ORS (75%). In Kenya, the situation was reversed: ORS (89%) was more likely to be used on recommendation than antibiotics (77%). The data thus suggest that nearly a quarter of caregivers in Kenya used antibiotics without a recommendation from a health care provider or pharmacy worker (Online Supplementary Document, table s7).

Among health care workers and pharmacy staff in both countries, 82% or more agreed with the statement "mothers like to be given the most powerful treatments". Except for health care workers in Kenya, most also agreed that "antibiotics are the most effective treatment for diarrhea" (Online Supplementary Document, table s5). In rural areas of Kenya, pharmacy staff estimated that caregivers walk 7 km one–way, on average, to reach their pharmacy (n = 49), and they estimated that one half of their clients are mothers of young children under five years old (n = 34).

## Financial considerations and preferred product formats

In India, median spending on the last episode of diarrhea was US$ 2.70 (**Table 7**). Among rural respondents, many of whom were at the lowest socioeconomic levels, it was US$ 2.29. The largest share of spending went to 'doctors' for services. About 72% of caregivers paid for these services, spending a median US$ 1.80 (US$ 1.26 in rural areas). These services may have included fees for injections or administration of intravenous fluids, which typically account for a significant portion of spending in this category.

In India, the cost of antibiotics was the other main component of spending. Almost all caregivers (93%) who used antibiotics during the last episode paid for them. Median spending was US$ 0.90, both for all users and for rural users. Although most caregivers who used ORS paid for it (73%), median spending on this product was only US$ 0.27, both for all users and rural users. Spending of US$ 0.27 matches the observed rural price of a single 1L ORS sachet, the size typically used in India.

In Kenya, median spending on the last diarrhea episode was US$ 0.82 (US$ 0.70 in rural areas) (**Table 7**). The largest amount of spending was for antibiotics. Most caregivers (73%) who used antibiotics paid for them. Median spending for antibiotics was US$ 0.59 both for all users and rural users and was consistent with purchase of syrup presentations. Syrups accounted for 100% of rural pharmacies' fastest–selling antibiotics for diarrhea, with a median price of US$ 0.59 (rural pharmacy survey; n = 125 products and prices, n = 49 pharmacies). The consistency between caregivers' self–reported spending on antibiotics at last episode and the product and pricing data gathered from staff at rural pharmacies is noteworthy.

Almost half (43%) of Kenyan caregivers who used ORS reported paying for it. Median spending was US$ 0.47 for all users and was actually higher among rural users at US$ 0.59 (**Table 7**). These figures imply purchase of 2.6 and 3.3 sachets, respectively, at the prevailing unit price of US$ 0.18 for one 0.5 L ORS sachet (the typical size in Kenya; price from rural pharmacy survey, n = 49). The numbers of sachets purchased approach the quantity Kenyan public sector health care workers said they prescribe (median 4, n = 90).

Selling ORS in rural areas appears to carry more profit potential at the retail level in Kenya than in India (**Table 7**). In Kenya, the retailers' profit incentive is to sell either antibiotics or ORS – and preferably both – since each will provide equal gross profit of US$ 0.24. In India, the retailers' incentives are to focus first on selling services (eg, doctors' fees, which may often include injections) and antibiotics, whereas selling ORS offers only a minor boost to gross profit. It is important to remember that the treatment components (antibiotics, ORS, etc.) were used at last episode to varying degrees and purchased privately to different degrees, so the profit breakdown and totals shown in **Table 7** are only illustrative.

Caregivers' stated willingness to pay for a full course of "a treatment for diarrhea, considering you might need to use the product for 5 days" was consistent with their purchase behavior and estimates by health care workers and retailers. In India, caregivers' (n = 404) stated willingness to pay was a median of US$ 1.80 (interquartile range (IQR) = 2.8) vs spending on the last episode of US$ 2.70 (IQR = 2.9). Estimates of what caregivers would be willing to pay by health care workers (median US$ 1.80, IQR = 2.7, n = 134) and pharmacy staff (median US$ 1.80, IQR = 1.8, n = 121) were similar, and aligned to caregiver estimates.

In Kenya, caregivers (n = 401) said they would be willing to pay a median of US$ 0.60 (IQR = 0.82) vs spending on the last episode of US$ 0.82. Estimates by pharmacy staff (US$ 1.20, IQR = 1.8, n = 144) were higher than caregiver estimates while health care workers (median US$ 0.60, IQR = 1.2, n = 117) were more aligned with caregiver estimates.

When asked about preferred product formats, caregivers generally expressed a preference for a conventional ORS sachet or either of two ready–to–drink formats (Online Supplementary Document, table s8). There was a stronger preference for the conventional ORS–style sachet in India (41%) than in Kenya (21%), and the combined preference for the two ready–to–drink formats was similar in the two

**Table 7.** Caregiver spending at last diarrhea episode and related profitability for rural private providers*

| Parameter | India | | Kenya | |
|---|---|---|---|---|
| | All | Rural | All | Rural |
| Carers who paid for health care services/other *and/or* treatments | 79% (n=397) | 79% (n=199) | 64% (n=352) | 63% (n=168) |
| Total spent, among all carers who paid (median) (IQR) | US$ 2.70 (2.9) (n=313) | US$ 2.29 (1.96) (n=158) | US$ 0.82 (1.4) (n=225) | US$ 0.70 (0.82) (n=105) |
| Treatments, spending – main components: | | | | |
| Antibiotics – of carers who gave at last episode,% who paid | 93% (n=238) | 94% (n=116) | 73% (n=189) | 62% (n=93) |
| Antibiotics – median amount spent at last episode (IQR) by carers who paid | US$ 0.90 (1.03) (n=221) | US$ 0.90 (0.68) (n=109) | US$ 0.59 (0.59) (n=138) | US$ 0.59 (0.35) (n=58) |
| Antibiotics – gross profit[a] (gross margin[b]) at retail–level, rural | | US$ 0.23 (25%)[c] | | US$ 0.24 (41%)[d] |
| ORS – of carers who gave at last episode, % who paid | 73% (n=190) | 71% (n=97) | 43% (n=156) | 29% (n=77) |
| ORS – median (IQR) amount spent at last episode, among carers who paid | US$ 0.27 (0.25) (n=139) | US$ 0.27 (0.20) (n=69) | US$ 0.47 (0.47) (n=67) | US$ 0.59 (0.35) (n=22) |
| ORS – gross profit[a] (gross margin[b]) at retail–level, rural | | US$ 0.09 (33%)[c] | | US$ 0.24 (41%)[d] |
| Healthcare services/other, spending: main components | | | | |
| India – "Doctors fees"[f]: carers who paid fees at last episode, as% of all | 72% (n=404) | 74% (n=202) | | |
| India – "Doctors fees"[f]: median (IQR) spending at last episode | US$ 1.80 (2.7) (n=290) | US$ 1.26 (0.9) (n=149) | | |
| India – "Doctors fees"[f]: profit[a] (gross margin[b]) at retail–level, rural | | US$ 0.58 (46%)[e] | | |
| Kenya – median (IQR) "card registration fees" [g] (occasional public–sector user fee) | | | US$ 0.35 (0.35) (n=36) | US$ 0.35 (0.35) (n=26) |
| Profitability analysis, retail–level: typical carer purchases, rural | | | | |
| Total gross profit[h] – when carer purchases all of above[i] (illustrative) | | US$ 0.90 | | US$ 0.48 |
| Share of total gross profit from ORS, in this scenario: | | 10% | | 50% |

ORS – oral rehydration solution

*R2 survey except where otherwise noted. See also Methods for how caregivers' spending was recorded. Notes: [a]Calculated as median amount spent x gross margin; [b]Gross margin taken here as equal to [(Revenue) – (Cost of materials)]/(Revenue) and excludes cost of labor, transport, rent, etc; [c]India – estimate from discussion with pharmaceutical executives by PATH, n=3; [d]Kenya rural pharmacy survey, n=49; [e]Radwan [14], 2005; [f]The "doctors fees" category was prominent in India results and included fees for injections or administration of intravenous fluids, which typically account for a significant portion of spending with private practitioners in that country; [g]This category is specific to Kenya results, and represents the co–pay sometimes charged by public clinics, which then provide a consultation and treatments (e.g., ORS), if in stock, for no added cost; [h]Gross profit accruing to private pharmacy in Kenya, and in India accruing directly to the private health–care worker and their affiliated pharmacy (in India, 65% of private health–care workers stated caregivers would obtain the products they prescribed either from their own practice (44%) or an affiliated pharmacy (21%; n=63)); [i]Sum of gross profits for antibiotics, ORS, and (in India) doctors' fees. Amounts shown in US dollars (US$), based on current exchange rates: India, 55.4 INR=US$ 1; Kenya, 84.7 KSH=US$ 1.

countries (42% and 49%, respectively). There was modest interest in a syrup presentation and minimal interest in either a self–dispersing tablet presentation or an alternative sachet style.

## DISCUSSION

### Caregivers' primary treatment goal is to stop diarrhea

Caregivers give treatments they believe will treat the diarrhea. Strikingly, the most frequent expectation of either antibiotics or ORS was that these treatments would stop the diarrhea. This motivation accounts for a substantial proportion of the actual use of ORS even though the real benefits of ORS center on rehydration. Although this finding contrasts with the results of some other surveys [11], caregivers' emphasis on treating the diarrhea has often been reported [12]. The use of multiple treatments by many caregivers – especially common in India – may derive in part from caregivers' perceptions that several of the main treatments are efficacious against the diarrhea itself. To state it simply, while many caregivers give antibiotics primarily to treat the diarrhea itself and very few perceive a rehydration benefit with antibiotics, their use of ORS or SSS may be driven as much by perceived efficacy against diarrhea as by rehydration goals. The widespread use of antibiotics is consistent with the alignment between caregivers' emphasis on treatment and their perception that antibiotics are the most effective and strongest medicine for diarrhea.

Several issues related to the timing, sequence, and the number of treatments given at last episode are worth highlighting. Although many caregivers in Kenya gave only one treatment, many in India deployed the proverbial 'kitchen sink' of treatments. Each of these patterns may provide distinct challenges for product promotion initiatives. For example, when caregivers are accustomed to giving one treatment, it may be hard to displace incumbent treatments or to catalyze demand for consistent use of both ORS and zinc (instead of one or the other).

If home remedies were used, they were typically started on the first day of the episode, and products such as antibiotics and ORS were typically started on the second day and continued for 3 days (4 days for antibiotics in Kenya). Because most episodes of diarrhea are self–limiting and typically last only 3 to 4 days, caregivers may form incorrect perceptions of the efficacy of some treatments. That is, caregivers may assume that the diarrhea stopped because of treatments being given at the time. There are several implications for intervention design. For example, promoting rapid initiation of ORS may be counterproductive to caregiver demand for ORS unless equal emphasis is placed on sustaining use through the episode. Also, promoting the benefits of ORS may be counterproductive if this focuses too narrowly on the rehydration benefit and so creates dissonance with the perception of many existing ORS users that the product helps treat diarrhea (possibly eroding use or users' potential to function as effective product advocates).

Although caregivers' primary focus is on treatment of diarrhea, the results of our interviews show that almost all caregivers understand that children with diarrhea need more fluid and that ORS helps replace fluid and minerals lost to diarrhea. This is important in part because some public health advocates may assume this is not understood, as did many of the providers surveyed.

## Inappropriate treatments are strongly entrenched

Use of inappropriate treatments was widespread, consumed most of caregivers' spending on treatment, and represents the expected standard–of–care from the viewpoints of both providers and caregivers. These widely documented [11,13,14], and well–established behaviors constrain the potential for correct and consistent use of ORS (and zinc) by diverting caregivers' limited time, money, and energy.

Indian caregivers' high spending was noteworthy. They obtained most treatments and health care services from private sources at last episode. The largest component of spending was for payments to private practitioners. We suspect a substantial share of this spending likely went for injections and intravenous fluids administration, based on reports of practices typical in India, consistency with the spending levels we observed, and private–practitioners' tendency to charge principally for injections and medicine rather than the consultation itself (Anna Stratis, personal communication, 2012) [15]. For example, Bhatia reported injections were given in two–thirds of 451 private–sector consultations [16], and Ashwath reported half of 64 children attending an outpatient–hospital clinic received an injection for an illness within the previous month [17].

The higher spending per episode in India may help to explain why Indian caregivers typically started treatment more quickly and used more treatments (including more homemade treatments such as SSS, very early in the episode) than their counterparts in Kenya. That is, Indian caregivers' may be trying more energetically to head off the diarrhea episode before it progresses and occasions what they know to be a costly set of treatments.

In Kenya, outlays per episode were still substantial relative to caregivers' limited incomes, although these costs are clearly much lower than they would be absent the subsidized care and treatments from the public sector. Our results illustrate one potential benefit of the relatively more involved public sector as seen in Kenya, and that is the norming effect such public services can have when they are provided widely. When Kenyan caregivers did need to purchase ORS privately, they typically purchased about 3 sachets of 0.5 L, approaching the number of sachets they would typically receive from public sources and spending a substantial US$ 0.47 to US$ 0.59 to do so.

A corollary observation is that the antibiotics used were typically not much more expensive than a course of ORS in the private sector, even before considering the time–and–effort costs of administering ORS or availability of antibiotic tablets that often cost less than a sachet of ORS [12,13,18]. This is important in part because some public health advocates may assume ORS is much less costly than antibiotics.

The results suggest caregivers, health care workers, and pharmacy retailers are conditioned to the now–routine use of antibiotics with pediatric diarrhea. Caregivers rank antibiotics ahead of ORS as the most effective treatment against the cause of diarrhea and as the strongest medicine. Caregivers may play an important role influencing providers' treatment recommendations. After all, and as illustrated in rural Kenya, mothers of young children form a large part of pharmacies' 'customer base' and often must walk many kilometers to visit a pharmacy (ie, they may not be inclined to go home 'empty handed' or with ORS only). Most providers felt their clients want to receive the most powerful medicines, and (like caregivers) most of them felt antibiotics are the most effective medicine for diarrhea in young children. Although most Kenyan health care work-

ers disagreed that antibiotics are the most effective treatment, approximately half of the antibiotics used by Kenyan caregivers at last episode were obtained from public facilities like those where most of the health care workers interviewed in Kenya were employed. The difficulties experienced by provider–training initiatives on treatment of pediatric diarrhea in developing countries [19] are consistent with our conclusions. Profitability also plays a role but to a lesser extent than is often imagined; for example, in Kenya the public sector provided about half of the antibiotics used to treat recent episodes of pediatric diarrhea.

The emergence of antibiotic (over)use as an established norm, and the role of client expectations, is not isolated to developing countries or to diarrhea. An example from the United States offers striking parallels. In the United States, sinusitis is the fifth leading driver for antibiotic prescriptions even though about 80% of cases will cure without medication and viral infections cause up to 98% of sinusitis. However, "antibiotics are prescribed more often than not, which reflects patients' expectations and the problem of differentiating viral from bacterial sinusitis in the primary care setting" [20].

The common use of antibiotics raises health and safety concerns, as do indications (in India) of widespread use of injections. Our results are consistent with reports on the overuse of antibiotics and contributing factors [21], both with diarrhea and generally [22-24]. Taken together, these raise important concerns about the potential development of antibiotic resistance [25,26]. In Kenya, the frequent use of antibiotics without any rehydrating therapy is worrisome. If zinc were to displace antibiotics, it might be administered without ORS or SSS. Finally, the possible widespread use of injections by private practitioners in India raises obvious safety concerns, emphasizing the potential for tragedies similar to those described in press reports [27].

## Satisfaction with ORS is high, but dosing is a challenge

An encouraging finding is the strong pattern of re–use of ORS by caregivers, who seem substantially satisfied with the product. If a caregiver had any previous experience using ORS, she typically obtained and used ORS during the last episode. This suggests that ORS product innovations such as taste improvements or packaging enhancements may offer less scope for improvement in ORS coverage than facilitating (first) use experiences and access among target populations.

Strikingly, both ever– and never–users of ORS held quite positive perceptions of ORS. This is consistent with the high rate of use of ORS at last episode among caregivers who had ever used ORS. The few concerns expressed mostly related to the volume of liquid, the (related) need to administer ORS too frequently, and often having leftover liquid that is wasted.

When caregivers did use ORS, most gave a relatively small volume of the solution each day at the peak of the episode, and most felt it was all they could manage to administer. Concerns about the volume of liquid and the frequency of administration were prominent among caregivers in both countries. Simply put, caregivers feel that the recommended dosing of ORS is impractical and overly ambitious, and they are giving less. Our results were consistent with previous reports on under–dosing of ORS [28]. The disconnect between the recommended dosing of ORS (geared towards particularly acute diarrhea, such as with cholera) and what is practical for caregivers dealing with more typical diarrhea may challenge caregivers' feelings of self–efficacy, creating disincentives to rapid initiation of ORS and correct use. Research to investigate a more practical yet sufficiently effective dosing regimen may be warranted. Because our results raise doubt on correct use, they call into question reliance on the simple metric of "ORS coverage", which only addresses consistency of use.

Preparation of the solution is another important aspect of correct use. Although we did not study this aspect of dosing directly, the data on low dosing of liquid, duration of use (3 days), and the number of sachets actually purchased (in India, only one) together suggest that many caregivers may be using ORS "a pinch at a time" and thus in highly variable concentrations. Other reports have indicated that problems with correct preparation of ORS are common [29,30].

Most caregivers in both countries preferred a 200 mL ORS pack size over a 1 L size (currently, typical pack sizes are 500 mL in Kenya and 1 L in India). The smaller pack size would help to address caregivers' concerns on wastage of leftover ORS. While many were attracted to ready–to–drink formats, the higher cost would likely limit uptake (this is the case in India, where ready–to–drink ORS is sold; reported use was low).

ORS is perceived as offering superior benefits compared to SSS, generally. ORS is perceived to offer the most balanced mix of expected benefits. It also ranked ahead of SSS on effectiveness and strength. Caregivers appear somewhat split on whether ORS or SSS is more acceptable to children, with a lean towards SSS in India and towards ORS in Kenya. A substantial minority of Kenyan caregivers voiced concern on the taste of ORS but a majority ranked ORS first on acceptability to children, with many citing good taste. Strong majorities of Indian caregivers felt ORS has a pleasant taste, but more ranked SSS first for acceptability to children than did so for ORS. In both countries, partisans of ORS or SSS all typically cited good taste in their rationale. If there were a major underlying difference in acceptability, we would expect to see this reflected in dosing,

but the pattern of dosing amounts for ORS are broadly in line with dosing of SSS. If SSS had an advantage, we may also expect lower re–use of ORS among ever–users of ORS, but this is not what we observed. Experience and habits may play a powerful role in sustaining use of either ORS or SSS. Affordability and accessibility may be the primary advantages of SSS, so enhancing affordability and accessibility of ORS could be important to displace SSS use. However, it is not immediately clear what priority displacing SSS with ORS merits given the scale of problems such as antibiotic overuse, antibiotic use in the absence of any rehydrating therapy (in Kenya), or the potentially widespread use of unnecessary injections (in India).

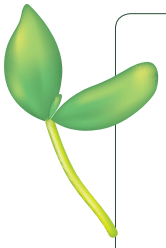
## Limitations

The study has some noteworthy limitations. First, the surveys were non representative because we used quota–sampling methods and excluded caregivers who were not aware of ORS. However, ORS awareness is high, we had many respondents from diverse settings and socioeconomic strata, and the results are highly consistent. Second, resource limitations prevented a second–round survey of providers. Third, we did not attempt to record co–morbidities or severity of diarrhea at last episode because of concerns about reliability and the expected low incidence of severe cases. Fourth, we did not measure response rates. Fifth, a caregiver's recall of a diarrhea episode that occurred up to two months ago may be inaccurate. However, it is expected that many individual–leve-l inaccuracies cancel out with respect to the summary statistics reported, and every effort was made to avoid introducing systematic biases. Also, recall–based results were remarkably consistent with other results. These considerations mitigate concerns about the reliability of information based on recall.

While this study was implemented in both India and Kenya, it was not designed as a comparative exercise per se. The reader should use caution in interpreting any apparent national–level differences.

Other factors also need to be considered when interpreting the results. For example, some caregivers may not have known what medicines they gave–a particular concern in differentiating antibiotics from antimotility drugs. However, the reported durations of antibiotic administration (median 3 days in India, 4 days in Kenya) and of diarrhea episodes (continuing, on average, for 3 days after initiation of antibiotics) are inconsistent with what would be expected had modern antimotility drugs (eg, loperamide) been given. Further, the amounts spent on antibiotics were consistent with purchase of syrup presentations, which are often preferred and are sold in single–course bottles that are more readily distinguishable than tablets. Extensive pretesting found respondents easily chose treatment categories from the visual cards used. When interviewers presented the visual cards for each category they also mentioned some common drugs as examples, such as the Flagyl and Norflox/Oflox trade–name antibiotics often used with diarrhea in Kenya and India, respectively. While all of these considerations mitigate concern on reliability of recall of drugs, this remains a limitation given the variety of drugs and variable knowledge of caregivers.

In India, we decided not to probe into the use of injections or intravenous drips, given concern that the complexities of studying these practices would spread the survey too thin. However, the high spending on "doctors fees" recorded in round 2 was a surprise and may indicate widespread use of injections and intravenous drips. This deserves further research.



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**Authorship declaration:** GZ contributed to the conception, design, and implementation of the study; design of the statistical analysis; interpretation of results; and drafting of the first version of the report and its following versions. ES contributed to the conception and design of the study; interpretation of results; and drafting of the report. MM contributed to the design and implementation of the study; design and implementation of the statistical analysis; statistical expertise; administrative, technical, and logistic support; and drafting of the report.

**Competing interests:** All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no conflict of interest.

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# Scaling up access to oral rehydration solution for diarrhea: Learning from historical experience in low– and high–performing countries

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**Aim** This paper aims to identify factors that systematically predict why some countries that have tried to scale up oral rehydration solution (ORS) have succeeded, and others have not.

**Methods** We examined ORS coverage over time, across countries, and through case studies. We conducted expert interviews and literature and data searches to better understand the history of ORS scale–up efforts and why they failed or succeeded in nine countries. We used qualitative, pairwise (or three–country) comparisons of geographically or otherwise similar countries that had different outcomes in terms of ORS scale–up. An algorithm was developed which scored country performance across key supply, demand and financing activities to quantitatively assess the scale–up efforts in each country.

**Results** The vast majority of countries have neither particularly low nor encouragingly high ORS use rates. We observed three clearly identifiable contrasts between countries that achieved and sustained high ORS coverage and those that did not. Key partners across sectors have critical roles to play to effectively address supply– and demand–side barriers. Efforts must synchronize demand generation, private provider outreach and public sector work. Many donor funds are either suspended or redirected in the event of political instability, exacerbating the health challenges faced by countries in these contexts. We found little information on the cost of scale–up efforts.

**Conclusions** We identified a number of characteristics of successful ORS scale–up programs, including involvement of a broad range of key players, addressing supply and demand generation together, and working with both public and private sectors. Dedicated efforts are needed to launch and sustain success, including monitoring and evaluation plans to track program costs and impacts. These case studies were designed to inform programmatic decision–making; thus, rigorous academic methods to qualitatively and quantitatively evaluate country ORS scale–up programs might yield additional, critical insights and confirm our conclusions.

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Oral rehydration therapy (ORT) for dehydrating diarrhea came into routine use at Bangladesh's Cholera Research Laboratory (now ICDDR,B) in 1969. Nine years later, the World Health Organization recommended a

standardized version of the therapy – Oral Rehydration Salts, or ORS – for all acute watery diarrhea in children [1]. However, on average between 2006 and 2011, only one third of children with diarrhea in developing countries received ORS [2].

These low rates of ORS use are surprising given the emphasis given to this product in the years after its introduction. The product was one of the foci of UNICEF's "GOBI–FFF" selective primary health care strategy of 1982 (the "O" in GOBI refers to ORS) [3]. In the mid–1990s, ORS was similarly made the keystone of diarrheal disease management in WHO's "Integrated Management of Childhood Illness" initiative [4], and *The Lancet* child survival series of 2003 identified it as the single intervention available at that time with the greatest potential to save lives [5]. Yet throughout this period, ORS gained ground at a rate of just 0.6 percentage points per year (analysis based on data available online from UNICEF [6], MEASURE DHS [7] and other national surveys).

Twenty countries (out of a total of 96 with data from the standard surveys series that track ORS coverage, including Demographic and Health Surveys (DHS) [6] and Multiple Indicator Cluster Surveys (MICS) [8]) have entirely failed in promoting rational diarrhea management, with less than 25% of pediatric diarrhea episodes treated with ORS. Yet many other countries have done much better, with 29 countries using ORS in one half or more of all episodes, and eight countries using ORS in two–thirds or more of all episodes. As can be seen in the map (**Figure 1**), by this criterion, high performing countries are found in every region of the world. The vast majority of countries in sub–Saharan Africa, as well as many Indian states, have neither particularly low nor encouragingly high rates of ORS use, but rather fall somewhere in the middle.

The objective of the present study was to address the question: Why have some countries succeeded in scaling up ORS for diarrhea, when others tried and failed? We hypothesized that countries would be more likely to have been successful in scaling up ORS if they simultaneously: 1) made significant improvements to the standard product offering, including lowering the price; 2) conducted wide–reaching marketing campaigns; 3) acted to remove regulatory barriers to the sale and promotion of ORS in the private sector; 4) improved private provider knowledge of rational diarrhea management; 5) improved public provider knowledge of rational diarrhea management; 6) made a concerted effort to improve the regularity of supply; and 7) mobilized partner funding as well as taking country ownership of the program. Some of these concepts have been examined in previous case studies [1,9] but we are not aware of any other work that has examined all of them simultaneously. To test these hypotheses we reviewed peer–reviewed articles and grey literature and conducted key informant interviews to learn about the history of ORS scale–up in each of the selected countries, completed qualitative case studies using information obtained from literature searches and interviews, and quantitatively analyzed the findings from these sources.

## METHODS

We categorized every country with ORS coverage data into three categories: countries that exceeded 50% coverage for ≥5 years and now have achieved >66% coverage were defined as "sustained success" (**Table 1**); countries that achieved >50% coverage at one point in time, then saw reductions in coverage of at least ten percentage points were defined as "unsustained success" (**Table 2**); and countries never reaching ORS coverage rates of 25% despite targeted scale–up efforts were defined as "non–starter (failure)" (**Table 3**).

We did not expect coverage of ORS in any country to exceed 75% because the average duration of an episode of pediatric diarrhea is 3.1 days, and approximately 25% of all episodes are of such brief duration (or mild presentation) that they do not significantly contribute to mortality and morbidity [10]. Caregivers are therefore not motivated to seek treatment outside the home. Although ORS is recommended for all episodes [2], we view a use rate of 75% as the maximum level that can be achieved at a population level.

Nine countries were purposively selected for in–depth case studies, including Bangladesh [11], Guyana [12], India [13], Madagascar [14], Malawi [15], Senegal [16], Sierra Leone [17], Tanzania [18], and Trinidad and Tobago [19]. These included all of the possible sustained successes ex-

**Table 1.** Countries meeting the criteria for "sustained" success

| Country | First year ORS coverage >50% | Most recent year ORS coverage >50% | Most recent coverage measured level | Total number of years coverage >50% |
|---|---|---|---|---|
| Bangladesh | 1994 | 2011 | 77.6 | 17 |
| Democratic People's Republic of Korea | 2000 | 2009 | 74.0 | 9 |
| Malawi | 2001 | 2010 | 69.1 | 9 |
| Sierra Leone | 2003 | 2010 | 72.6 | 7 |
| Thailand | 1996 | 2006 | 68.3 | 10 |

ORS – oral rehydration solution

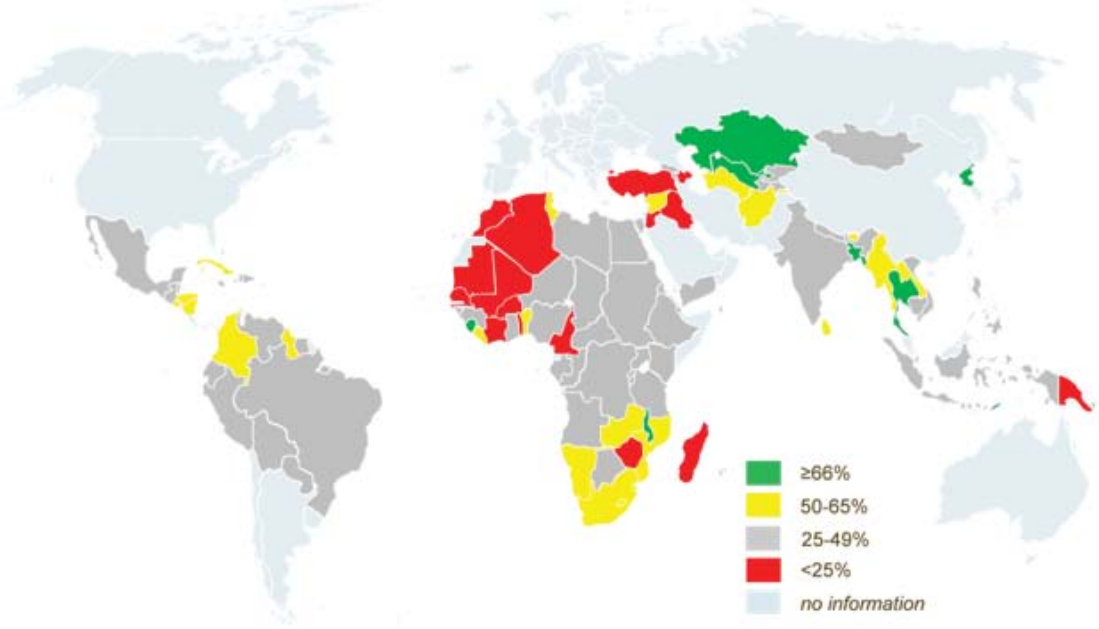



**Figure 1.** Map of ORS use rates around the world. (Data sources: Demographic and Health Surveys, Multiple Indicator Cluster Surveys and national survey series).

**Table 2.** Countries meeting the criteria for "unsustained success"

| Country | Maximum ORS coverage reached | Year maximum coverage reached | Subsequent decline in coverage | Most recent year ORS coverage reported* |
|---|---|---|---|---|
| Kazakhstan | 73.3 | 2006 | 11.5 | 2011 |
| Lesotho | 54.5 | 2000 | 12.1 | 2004 |
| Mongolia | 55.9 | 2000 | 17.9 | 2005 |
| Swaziland | 85.7 | 2007 | 28.1 | 2010 |
| Trinidad and Tobago | 52.3 | 1987 | 20.3 | 2000 |
| United Republic of Tanzania | 57.6 | 1992 | 13.9 | 2010 |

ORS – oral rehydration solution

*At time of classification for this study.

**Table 3.** Countries meeting the criteria for "non–starters"

| Country | Maximum ORS coverage reached | Number of data points |
|---|---|---|
| Burkina Faso | 21.2 | 5 |
| Cameroon | 21.9 | 5 |
| Chad | 23.4 | 4 |
| Côte d'Ivoire | 22.7 | 5 |
| Madagascar | 23.1 | 4 |
| Mali | 15.7 | 3 |
| Mauritania | 23.3 | 2 |
| Morocco | 24.4 | 3 |
| Senegal | 22.4 | 5 |
| Togo | 20.2 | 5 |
| Turkey | 15.9 | 2 |
| Zimbabwe | 20.9 | 3 |

ORS – oral rehydration solution

cept for the Democratic Republic of Korea, where we knew that we would not be able find relevant information, and Thailand, which was excluded arbitrarily. We matched these successes to one "non–starter" country which was geographically close by and plausibly comparable in terms of size and health system organization. India was included as a historic comparator for Bangladesh because it was a "non–starter" until 2005, even though coverage has improved since that time; because of its subsequent change in status, when we scored this country for the quantitative analysis we only considered events up to 2005. Tanzania was studied as an interesting case of an "unsustained success" which could reasonably be compared to both Malawi (a "sustained success" scale–up country) and to Madagascar (a "non–starter"). In order to include a pair of case studies from the western hemisphere–where no country has

reached our standard of "sustained success"–we included Guyana, where coverage reached 49.8% in 2009, and compared it to Trinidad and Tobago, a clear "unsustained success". We conducted similar case studies of zinc uptake in four countries, including Bangladesh [20], Madagascar [21], Nepal [22], and Tanzania [23]. However, because there is more information and longitudinal data, we focused this manuscript on ORS scale–up.

In each country, literature reviews and expert interviews were conducted to better understand the history of ORS scale–up efforts and why they failed or succeeded. The review included peer–reviewed articles, conference presentations, and grant reports available to the Bill & Melinda Gates Foundation and partners. An initial search was conducted in PubMed in April 2012 and the titles and abstracts of all the retrieved citations were examined for relevance to ORS scale–up efforts in each country. Following the initial search, multiple searches were conducted in PubMed and Google through October 2012 to identify studies and reports related to ORS scale–up in the selected countries. The search strategy was restricted to documents written in English and French. The following keyword terms (in English) were used with each country: ORS, ORT, and diarrhea.

Additional articles and reviews related to the relevant topics were identified by hand–searching the references in the articles and reports identified through the search engines. We also sought additional literature from the United Nations Children's Fund [24], the World Health Organization [25], and the World Bank [26] websites. Reports from USAID (United States Agency for International Development)–funded projects were retrieved from the USAID Development Experience Clearinghouse [27].

Data for a wide range of monitoring and impact evaluation indicators in the areas of population, health, and nutrition were obtained from Demographic and Health Surveys [28], Multiple Indicator Cluster Surveys [29], and Malaria Indicator Surveys [30]. Information about the characteristics of health facilities and services available in a country was obtained from Service Provision Assessment Surveys [31]. Data on drug prices, availability and affordability were obtained from the World Health Organization/Health Action International surveys and reports [32].

The "snowball" technique was used to identify informants. An initial list of potential key informants was generated through personal communication with experts in the field of diarrhea management, with the aim of interviewing individuals from a range of sectors to provide a broad range of perspectives. Potential key informants from governments, donors, multilateral and bilateral organizations, non–governmental organizations (NGO), the local private sector, and academic and clinical institutions were contacted individually via email to request telephone or, in some cases, in–person interviews. Between April and September 2012, key informant interviews were conducted with 58 experts (**Table 4**) to understand what efforts were made improve ORS use in the past, and how, with the benefit of hindsight, well–informed observers think these efforts could have been better designed in each of the nine countries. The interviewers took notes during and after the interviews to document the key informants' responses.

An interview tool (Online Supplementary Document) was developed to guide the discussion and to ensure that the primary questions were answered. Semi–structured interviews were used to elicit open–ended responses. Not all interviewees were asked exactly all the same questions despite utilization of the same interview guide, given the semi–structured nature of the interviews, and that differing perspectives were sought from each type of partner. We circulated the draft case studies to local key informants with requests for their review and comment. The case studies were finalized following this validation.

The team used qualitative, pairwise (or three–country) comparisons of geographically or otherwise similar countries that had different outcomes in terms of ORS scale–up. In addition to the qualitative pairwise (or three–country) comparisons of country case studies, the scale–up efforts in each country were quantitatively assessed, based on a numeric scoring of country performance across various key supply, demand and financing activities. For each case study, we scored the country on their efforts along seven dimensions of implementation, with a range of scores from 0 (low/no effort) to 2 (high effort). The sum of these scores yields an implementation score ranging from 0 to 14. The seven dimensions of implementation included the following: made significant improvements to the standard product offering, including lowering price; conducted wide–reaching marketing campaigns; acted to remove regulatory barriers to sale and promotion of ORS in the private sector; improved private provider knowledge of rational diarrhea management; improved public provider knowledge of rational diarrhea management; made a concerted effort to improve the regularity of supply; mobilized partner funding as well as taking country ownership of the program.

The quantitative portion of evaluation was conducted through a scoring algorithm. Scoring was made as consistent as possible across countries by developing precise definitions of what was included in "0", "1" or "2" scores for each dimension (**Table 5**). Since not all countries had the same data availability, scoring definitions generally had 2–3 components so that countries with non–equivalent information could still be classified. After scoring each component, aggregate scores were calculated for each country by summing across components. A statistical test was conducted with the aim of rejecting the hypothesis that there

**Table 4.** Dimensions of implementation and their scales

| Dimension | Definition | Scale |
|---|---|---|
| Political stability | The degree to which a country has had minimal political conflict, civil unrest and/or violence | High–Medium–Low |
| Natural disasters | The number of natural disasters experienced by the country during the ORS or zinc scale–up time period | High–Medium–Low |
| U5 mortality | U5 No. deaths | U5 No. deaths |
| U5 deaths due to diarrhea | U5 No. deaths due to diarrhea | U5 No. deaths due to diarrhea |
| Vaccine coverage | The immunization rate | % DTP3 |
| Zinc introduction | Whether the country has introduced zinc | Y/N |
| Private sector share | Of those seeking care for diarrhea, % going to private sector | % going to private sector |
| USAID recipient | Whether the country has received funding from USAID | Y/N |
| Home–based solutions promotion | Whether the country initially promoted home–based sugar–salt solutions | Y/N |
| IMCI country | Whether the country has introduced IMCI | Y/N |
| Decentralization of responsibility not funding | Whether the country has decentralized responsibility without also decentralizing funding | Y/N |
| Degree of collaboration across government, private, public | Extent to which partners worked together on diarrhea case management | HIGH – Multiple types of partners involved and collaborating<br>MEDIUM – Multiple types of partners involved but tense relations OR few partners but strong relations<br>LOW – No partnerships, or a few non–collaborative ones |
| Female literacy rate | Self–explanatory | % females literate |
| Diarrhea care–seeking | Degree to which caregivers sought treatment for diarrhea when their child fell ill | % seeking care |
| Reach of health system | Quality of the health infrastructure | HIGH – Infrastructure has broad reach and HCW capacity appropriate for pop size<br>MEDIUM – Broad reach OR appropriate HCW capacity<br>LOW – Insufficient reach and poor capacity |
| Surface area | Self–explanatory | square km |
| Population | Self–explanatory | No. people |
| SCALE–UP INDICATORS | | |
| Improved product, including pricing | Degree to which scale–up attempt improved the ORS or zinc product, including making it affordable | HIGH – Price not a barrier to purchase; consumer research conducted to determine preferences<br>MEDIUM – Generally strong product, but price or consumer research sub–optimally conducted<br>LOW – Pricing and product not informed by any prior information |
| Marketing campaign | Degree to which scale–up attempt conducted a successful direct–to–consumer marketing campaign | HIGH – Multi–channel, researched campaign of sufficient duration; consumer demand increased<br>MEDIUM – Multi–channel or of long duration; high knowledge low utilization<br>LOW – Little impact on awareness and/or use after the campaign |
| Regulatory approval | Whether regulatory hurdles were overcome | Y/N |
| Improved private provider knowledge | Degree to which campaign successfully got private providers to recommend ORS and/or zinc | HIGH – For areas where high use of private providers, specific interventions targeting private providers; for others, inclusion in outreach; positive impact on provider recommendations<br>MEDIUM – Inclusion in outreach, awareness but not impact<br>LOW – Not included in outreach |
| Improved public provider knowledge; increasing supportive supervision | Degree to which campaign successfully got public providers to recommend ORS and/or zinc | HIGH – For areas where high use of public providers, specific interventions targeting private providers; for others, inclusion in outreach; positive impact on provider recommendations<br>MEDIUM – Inclusion in outreach, awareness but not impact<br>LOW – Not included in outreach |
| Increasing availability of supply | Degree to which scale–up including local manufacturing, and consistent availability of quality product | HIGH – Few stockouts, local supplier, private and public<br>MEDIUM – Modest number of stockouts, foreign supply, private or public<br>LOW – Low availability |
| Financing of scale–up | Degree to which countries successfully began to own scale–up and both scale–up and maintenance had sufficient funds | HIGH – Partners contribute but country assume ownership; sufficient funding in volume and duration<br>MEDIUM – Partners contribute or country ownership, but funding insufficient<br>LOW – Few contributors; insufficient funding |

ORS – oral rehydration solution, U5 – under 5 years of age, DTP3 – Diphtheria–tetanus–pertussis, USAID – United States Agency for International Development, IMCI – Integrated Management of Childhood Illness, No.- number, Y/N – yes/no

was a trend in the aggregate scores across the three categories of countries (H1: $score_{sustained\_success} > score_{unsustained\_success} > score_{non-starter}$). The test used was Cuzick's non–parametric trend, which is an extension of the Wilcoxon rank–sum test [33]. Given that the scoring criteria demanded a certain degree of subjectivity in order to classify countries with different types of data, we urge caution in interpreting these results.

**Table 5.** Number and type of key informants accessed for each country

| Country | Government | Donor | Multilateral and bilateral | NGO | Local private sector | Academia | Clinical | Total |
|---|---|---|---|---|---|---|---|---|
| Bangladesh | 0 | 1 | 0 | 2 | 2 | 1 | 0 | 6 |
| Guyana | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 3 |
| India | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 4 |
| Madagascar | 1 | 0 | 0 | 7 | 0 | 0 | 0 | 8 |
| Malawi | 1 | 0 | 1 | 4 | 0 | 0 | 0 | 6 |
| Senegal | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 4 |
| Sierra Leone | 1 | 1 | 0 | 5 | 0 | 0 | 0 | 7 |
| Tanzania | 1 | 0 | 2 | 7 | 1 | 0 | 0 | 11 |
| Trinidad and Tobago | 0 | 0 | 3 | 1 | 0 | 0 | 2 | 6 |
| Multi–country input | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 3 |
| Total | 5 | 3 | 8 | 33 | 4 | 1 | 4 | 58 |

NGO – Non-governmental organization

**Table 6.** Scores given to each country for each scale–up criterion

| Scale–up indicators | Bangladesh | Malawi | Sierra Leone | Guyana | Tanzania | Trinidad & Tobago | Senegal | India* | Madagascar |
|---|---|---|---|---|---|---|---|---|---|
| Improved product, including pricing | 2 | 2 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| Marketing campaign | 2 | 2 | 2 | 2 | 0 | 1 | 0 | 1 | 0 |
| Regulatory not a barrier | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Improved private provider knowledge | 1 | 2 | 0 | 1 | 1 | 2 | 0 | 0 | 1 |
| Improved public provider knowledge; increasing supportive supervision | 2 | 1 | 2 | 2 | 0 | 2 | 1 | 1 | 1 |
| Increasing availability of supply | 2 | 2 | 2 | 1 | 0 | 1 | 0 | 1 | 1 |
| Financing of scale–up | 2 | 1 | 1 | 2 | 0 | 2 | 0 | 0 | 0 |
| TOTAL | 13 | 12 | 10 | 11 | 3 | 11 | 4 | 6 | 6 |

*Up to 2005

# RESULTS

## Country comparisons

Country comparisons are presented in **Figure 2**.

**Comparison 1: Sierra Leone vs Senegal.** The West African country of Sierra Leone, mired in civil war from 1991–2002, is a perhaps unexpected example of sustained, successful scale–up. Even before the civil war, Blue Flag Volunteers (BFVs) were trained to promote hygiene and treat diarrhea with ORT. During the conflict, which displaced as many as 2 million out of the 5.5 million population, ORS was pushed heavily on displaced populations in camps. After the civil war, the primary health care system was "reinvented", with multi–donor support. Recurrent cholera outbreaks were managed with ORS and efforts were made to ensure that the supply chain was maintained at each level: the Ministry of Health and Sanitation increased the intensity of tracking ORS distribution, districts and communities were in charge of ordering supplies, and peer supervisors facilitated re–stocking ORS in Community Based Distributors' (CBDs) kits. The population learned about the product via interpersonal communications with very active community promoters (BFVs and or CBDs). Integrated community case management of childhood illness was introduced to some districts in late 2000s and free health care for pregnant and lactating women and children under–five was introduced in 2010 [34–37].

Senegal is a West African country of 13 million people where ORS scale–up efforts have not succeeded ("non–starter"). The country is very stable, with a well–organized health system and relatively good infrastructure. The United States provided over half of all bilateral aid for health (basic) in the 2000s. USAID has been promoting ORS in Senegal since 1985, through multiple, successive, standalone "Technical Assistance" programs in "USAID regions" in the West – including PRITECH (1985–1993), BASICS (1994–2006), Child Survival Program (1998–2002), Fatick Partnership (2007–2009), Community Health Program (2006–2011). UNICEF supplied all ORS in the country until 2000 and Integrated Management of Childhood Illness (IMCI) was introduced in the 2000s, but the guidelines resulted in no change in clinical practice. The "health hut" program was launched in the late 1990s, including activities to promote both ORS and home fluids (including sugar–salt solution). However, ORS was not widely avail-

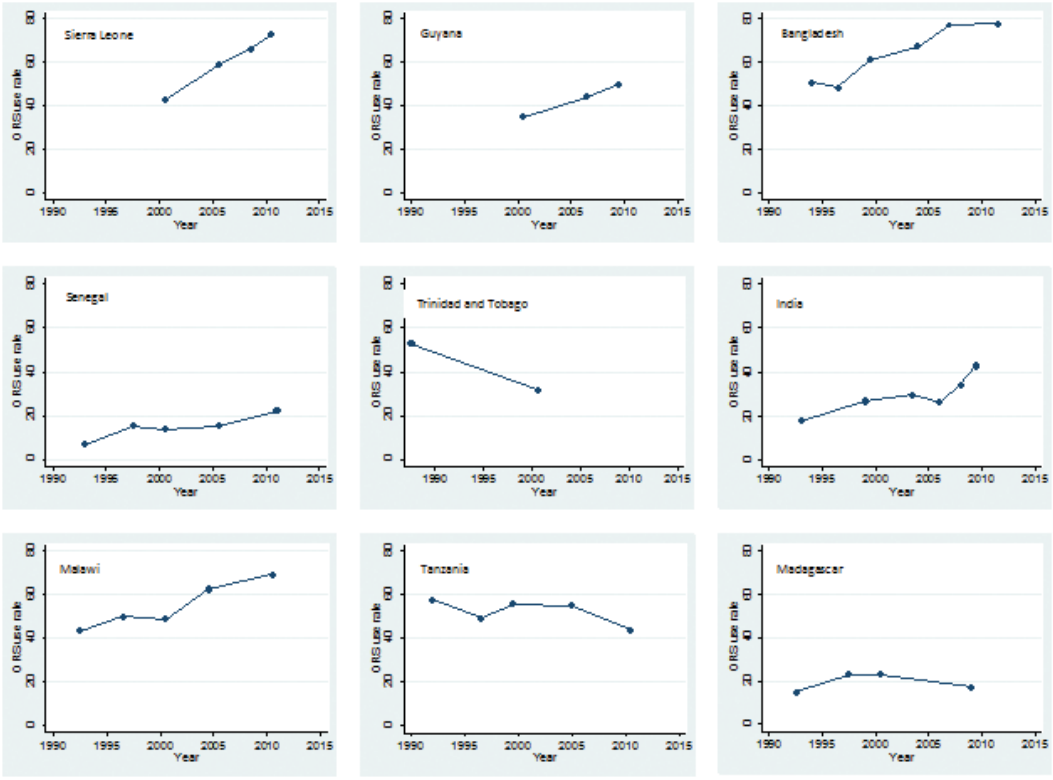



**Figure 2.** Oral rehydration solution (ORS) use rates by country, 1987-2011.

able in Senegal due to a weak distribution system that caused frequent shortages and stock–outs: availability of essential drugs was highest at the storage facilities and decreased at the more peripheral health facilities [38]. There are now 1600 health huts in Senegal, but they recover the full cost of medicines and, when surveyed, few (6–47%) health providers knew how to correctly look for signs of dehydration [39].

There are four key lessons from this comparison. First, interpersonal communications led to universal familiarity with ORS in Sierra Leone, whereas 41% of the population in Senegal still does not know about this product [40]. In Sierra Leone, emergencies provided an opportunity for boosting confidence in the product, and its purpose (rehydration, not symptom relief) is understood and appreciated. This understanding has been undermined in Senegal by mixed messaging about the benefits of ORS vs sugar–salt solution.

Second, basic supply chain management kept ORS widely available in Sierra Leone; in Senegal, it was unavailable in the private sector because ORS does not have a "visa" required to register drug products [36] and therefore could not be sold as a medicine, and public sector availability was also inconsistent. Further, pricing favored ORS in Sierra Leone, where the product is cheaper than in Senegal and where the cost of sugar made home–produced alternatives unaffordable (also not the case in Senegal). Finally, the regional stand–alone project approach of USAID in Senegal appears to have been too limited in scope and scale to increase ORS usage, compared to the "national reconstruction project" in Sierra Leone, launched with lots of donor support to restore infrastructure and health services, and through which a comprehensive community case management program was created. Key informants suggested that there was limited government spending on scale–up efforts in Senegal during the period under consideration.

**Comparison 2: Guyana vs Trinidad and Tobago.** Guyana is a "sustained success" country of just 742 thousand people, in South America but culturally of the Caribbean. The country is susceptible to flooding and experienced a cholera epidemic in 1992 [41]. After the 1992 cholera epidemic, Guyana created a national policy for the treatment of diarrhea, including ORS. The Ministry of Health purchased large quantities of ORS, including pre–mixed liquid, and stockpiled product for disasters. The country's dense network of public health centers and health posts was supplemented by 287 Community Health Workers who extended the reach into deep rural areas and demonstrated correct use of ORS. According to key informants, the Ministry of Health conducted yearly, seasonal marketing for ORS, using newsprint, television, and radio and made ORS available free in the public sector.

Trinidad and Tobago is an "unsustained success" Caribbean country of 1.2 million people and is relatively wealthy

with abundant oil and gas. Key informants recalled that a single local champion established Oral Rehydration Units in three major hospitals/health centers in the capital in 1981, in conjunction with an early 1980s ORS marketing campaign funded by the International Development Research Center (IDRC, US$ 132 thousand), which used a logo on printed materials and also ran radio and television spots. One radio station hosted a call–in program with health care providers and focused on diarrhea prevention. Key informants suggested that the campaign was intended to be both relevant to and empowering for mothers, and relied on mother–to–mother interpersonal communication to disseminate messages. Messaging switched to promoting "rehydration", and there was even distracting debate over merits of coconut water as a source of liquidand electrolytes [42]. Ultimately, scale–up of water and sanitation improvements has been associated with a major reduction in diarrhea incidence; diarrhea is no longer seen as national priority since diarrheal disease accounted for less than 1% of deaths among children under–five in 2010 [43].

This comparison illustrates that ORS is very hard to promote if it is not epidemiologically relevant. Although both countries experienced declines in mortality to low levels, ORS retained relevance in Guyana because of repeated outbreaks of diarrheal disease after flooding. This comparison underscores the essential nature of broad national buy–in. The program in Trinidad and Tobago relied on one person and external funding, whereas Guyana has embraced ORS as part of its commitment to universal primary health care, with the government even taking on responsibility for regular communication campaigns. Finally, clarity of message is essential. In Trinidad and Tobago, the messaging was inconsistent between ORS, breastfeeding, and even coconut water, whereas Guyana made a strong and lasting commitment to ORS, and folded this seamlessly into integrated programs such as Integrated Management of Childhood Illness (IMCI).

**Comparison 3: Malawi, Tanzania and Madagascar.** Malawi is a land–locked country in Eastern/Southern Africa with 16.3 million people and successfully sustained scale–up. The country has never had significant civil unrest or natural disasters. Malawi implemented a National Control of Diarrheal Disease Program in 1985 and stopped promoting sugar–salt solution in 1989, using multiple channels to popularize ORS (so that 90% of the population was familiar with it by 1992). Integrated Management of Childhood Illness (IMCI) was rolled out comprehensively to all districts and a cadre of "Cholera Assistants" was instituted in the 1970s. These were developed into Health Surveillance Assistants now present in all "hard–to–reach" communities of the country [44]. From the early 2000s, USAID funded Population Services International (PSI) to socially market branded ORS, achieving universal recognition, and massive penetration of pharmacies and retail outlets. The product was free in the public sector and heavily subsidized in the private sector [45].

Tanzania has 46.9 million people and was classified as an "unsustained success" for ORS scale up because it achieved greater than 50% coverage and then declined. Tanzania implemented a National Control of Diarrheal Diseases Program in the 1980s, with "Diarrhea Treatment Corners" in health centers and hospitals and achieved 93% familiarity with ORS by 1991 [46]. The IMCI Strategy was gradually rolled out and evidence from a local trial showed that IMCI did not improve ORS use [47]. Although ORS was widely available in the public sector in 2006 [48], availability appears to have fallen (to 57.4%) by 2009 for unclear reasons [49]. A local producer (Shelys) did little to stimulate demand, relying on public tenders; the second local supplier went bankrupt in 2008. USAID–funded outreach to pharmacists and Accredited Drug Dispensing Outlets (ADDOs) resulted in good availability from the early 2000s, but conducted little marketing beyond these segments [50]. There was little direct–to–consumer marketing of ORS in Tanzania except through USAID's Point–of–Use Water Disinfection and Zinc Treatment (POUZN) project (2005–2010) which was all non–branded promotion and time–limited [51]. Unlike Malawi, Tanzania lacks a community health worker program at scale. ORS is not always free in the public sector and there is no subsidy.

Madagascar is an island of 22.0 million people and was classified as a "non–starter" for ORS scale–up because it never reached greater than 23.1% coverage. It has experienced a relentless series of natural disasters, and, in 2009, widely perceived to have been unconstitutional transfer of power. There was no ORS in country at all until 1988. UNICEF then supported a local producer with limited capacity, which eventually went out of business, leaving the country wholly dependent on imported supply. While many countries import health products, key informants suggested that the frequency with which Madagascar experienced natural disasters and the political turmoil that led to import disruptions resulted in poor accessibility of ORS. Early radio campaigns promoted both ORS and home–made sugar–salt solution. USAID supported co–packaged products only through the POUZN Project from 2008 to 2010 but diverted support to non–government entities following a transfer of power, which severely weakened program efforts to scale–up ORS [52].This diversion likely contributed to the poor penetration of programs for training public providers and community–based distribution, which reached <10% and 15%, respectively, of the country.

This comparison reveals that once universal familiarity with ORS is achieved, availability is extremely important. Malawi achieved very high levels of availability in both public and

private sectors, whereas in Madagascar, uptake has been crippled by lack of availability. In Tanzania, the weakening public sector supply chain may explain recent declines in ORS use. An organized cadre of trained community–based distributors can greatly extend the reach of the public sector to achieve market penetration at scale. It is possible to capitalize on floods and cholera epidemics to increase familiarity with and trust in ORS, but countries enmeshed in political unrest are not conducive to ORS scale–up. Reliance on a single donor is risky because support may be abruptly terminated before programs are mature.

**Comparison 4: Bangladesh vs India.** Bangladesh, a South Asian country of 161 million people, was the first country in the world to accumulate large–scale experience using ORT. It is home to the world renowned International Centre for Diarrhoeal Disease Research (ICCDR,B). ICDDR,B developed ORT and continues to research and promote the approach, modeling successful control of diarrhea mortality. In 1981, the government created the National Oral Rehydration Project and distributed packets of ORS to health centers in 100/509 sub–districts [53]. Between 1980 and 1990, BRAC (formerly Bangladesh Rural Advancement Committee) trained 12 million women (approximately half of all women in the country) in preparation and use of sugar–salt solution, and still trains community health workers [51]. Bangladesh explicitly switched from promotion of sugar–salt solution to promotion of ORS. Starting in 1985 Population Services International (PSI) and, later, the Social Marketing Company (SMC) promoted branded ORS through multi–channel social marketing, spending US$ 1million/year and capturing 80% of the market. In the early 2000s, SMC built its own manufacturing facility and services 220 000 retail outlets [54]. According to key informants, in addition to SMC, there are now 30–40 ORS suppliers. ORS is supplied for free in the public sector and is very cheap in the private sector (US$ 0.06) [52]. Bangladesh relied on the family unit to sustain ORS use – the majority of mothers now educate their children on ORS, removing the need for repeated marketing campaigns. The most recent DHS survey provides clear evidence of successful ORS scale–up efforts: 77.6% of recent diarrhea episodes were treated with ORS (and 40.8% were treated with zinc), and only 2.0% of all under–five deaths were attributed to diarrhea [55].

India's 1.2 billion people reside in 28 states and seven Union Territories, each with hugely different public health systems and health outcomes. India was classified as a "nonstarter" through 2005 then had dramatic increases in coverage. India's multiple large scale government programs–including Diarrheal Disease Control Program (1978), Child Survival and Safe Motherhood Program (1992), Reproductive and Child Health Program (1997), and National Rural Health Mission (2005)—have resulted in high ORS availability in the public sector and training and stocking of outreach workers such as Anganwadi Workers and, more recently, Accredited Social Health Activists (ASHAs). In the 1980s, UNICEF promoted sugar–salt solution [56], which is still more familiar and more widely used than ORS. There is no national consensus in favor of ORS. The Program for Advancement of Commercial Technology–Child and Reproductive Health (PACT–CRH), a US$ 30 million USAID project, began strong promotion of ORS in the mid–2000s, with celebrity partnerships, media, home visits, and free samples [57]. India's vibrant pharmaceutical industry actively markets antibiotics to private providers, who command at least two–thirds of the market [58]. Public health detailing to private providers has never been done at scale.

This comparison underscores that even in countries where the market for diarrhea treatment is dominated by the informal private sector; it is possible to achieve high levels of use of ORS by changing social norms. It is likely that intensive interpersonal communication is a critical part of this behavior change, and it is also important to directly reach frontline providers at scale. Conversely, an excessive emphasis on public sector providers, in a context where, according to key informants, the public sector is under–valued and under–utilized, is not likely to be very effective, at least in the short term. Branded marketing can be very helpful, but must be explicitly directed at the mass market (India's most successful Electral brand has never been marketed as a product intended for self–treatment).Unambiguous messaging that home–made sugar salt solution is not an adequate substitute for ORS is critical for successful scale–up. Bangladesh benefited from the leadership of a highly respected local institutional champion for ORS (ICDDR,B) and managed to create a broad alliance of major local stakeholders. In India, the major champions of ORS have been mostly external, and there is no equivalent of BRAC that reaches beyond the public sector.

## Quantification of scale–up factors analysis

There was strong evidence that the aggregate scale up scores were more favorable in the countries that achieved more sustainable scale–up, ie, countries that exceeded 50% coverage for ≥5 years and now have achieved >66% coverage ($P = 0.042$, Cuzick's non–parametric test for trend; **Figure 3**). Although the very small sample size suggests caution when interpreting between group differences in individual implementation categories (**Table 6**), there is overwhelming evidence that the four successful countries all implemented well–researched, multi–channel communications campaigns, whereas this was not done at all in the two "non–starter" countries, and only to a very limited extent in the three "unsustained success" countries. The

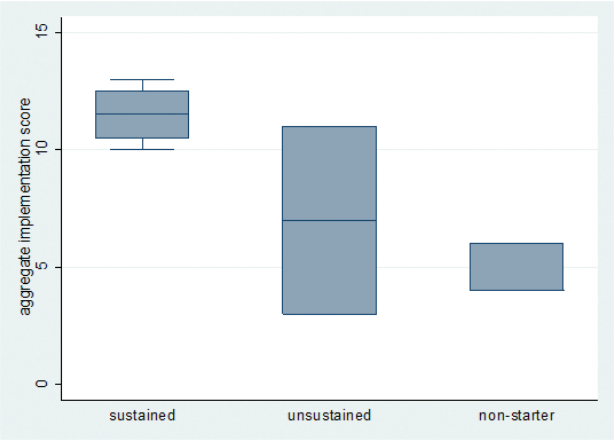



**Figure 3.** Aggregate implementation scores, by country scale-up type. Box plot with whiskers from minimum to maximum scores for the "sustained success" countries. The whiskers indicate the range of the data and are represented as vertical lines ending in a small horizontal line. The median and the interquartile range (IQR) were used to construct each box. The horizontal bar in the middle is the median score and the height of the box is equal to the IQR, drawn so that it starts at the 25th percentile (lower quartile value) and stops at the 75th percentile (upper quartile value).

next strongest association was with the financing of scale–up, where the more successful countries were more likely to have mobilized substantial funds from partners and taken significant ownership themselves.

## DISCUSSION

Since UNICEF placed ORS at the heart of its "GOBI–FFF" strategy in 1982, usage of ORS has increased slowly but steadily, suggesting a systematic response to public health recommendations [1]. Despite global efforts over the past four decades, however, current ORS use rates in the developing world are surprisingly low. While some countries have not succeeded in promoting rational diarrhea management and others have done much better, most countries are somewhere in the middle. This exercise was designed to explore the root causes of this diversity in ORS use, particularly focusing on direct and indirect contributors to ORS scale–up in countries with very high and very low ORS use rates.

Our initial hypotheses were mainly confirmed – that is, countries were more likely to have been successful in scaling up ORS if they (i) ensured both broad national buy–in and collaboration between government, non–government and private sectors; (ii) made significant efforts to synchronize demand generation, private provider outreach, and public sector work; and (iii) the context at the time of the interventions was conducive to scale up, including funding directed to ORS scale–up and the absence of political turmoil. We also drew some preliminary conclusions about specific elements of scale–up programs, though we believe these will need further validation. While these concepts are not entirely original and novel, we are not aware of any other work that has examined all of them simultaneously.

Key informant interviews suggested that partner collaboration was especially critical to success in Sierra Leone, Bangladesh and Guyana. The governments in all three countries collaborated with a range of development partners in the public and private sectors, reducing potential for "donor dependency". Senegal's reportedly weak government engagement in the early stages of ORS scale–up efforts and reliance on USAID were both cited by key informants as drivers of continuing low ORS use rates. Similar findings were reported from a case study in Philippines as our findings from Trinidad and Tobago: hospital admissions attributable to severe diarrhea declined and ORS became less epidemiologically relevant as income and sanitation improved [1].

The results of the quantification of scale–up factors analysis, despite relying heavily on qualitative information, suggested a correlation between high ORS use rates and synchronicity of demand– and supply–side interventions. All four "sustained successes" (Sierra Leone, Guyana, Malawi, and Bangladesh) focused on community–level delivery (although operationalized in very different ways), promoted ORS through health worker communications and mass media, provided ORS free of charge in public sector and had secure supply of the product. Malawi and Bangladesh have historically had robust community– and household–level interventions that highlight the importance of interpersonal communications to increasing uptake of ORS, and ensuring availability in areas close to where people live. Malawi also utilized tracking mechanisms to reduce stock–outs, and Bangladesh had a sales force for private sector outreach. "Non–starter" countries generally lacked coordinated, sustained efforts to improve supply and demand, and efforts were reportedly hindered by poor country ownership and insufficient financing. For example, the ADDOs in Tanzania can extend the reach of drug shops to rural areas, but given the vast distances in the country, gaps remain for certain segments of the population. Both Madagascar and, more recently, Tanzania struggled to maintain product availability at public health facilities, which may have contributed to low ORS use in those countries.

One of the most surprising findings was the importance of the context in which the scale–up efforts were implemented. The case studies show how clearly it played a role in the outcomes of scale–up efforts, and how there is no "one–size–fits–all" approach or program for ORS. The case study of Madagascar demonstrates how difficult it is to implement successful treatment programs when the health sys-

tem is passing through a period of acute destabilization. This highlights the importance of fully understanding the risks of working in potential high–impact, volatile countries, where the need is great but the risk of program disruption is very high. However, we should note that many of the countries that we included in the case studies were relatively stable compared to Madagascar, so further studies to support or negate this hypothesis, and to better understand how to successfully operate in high–risk, high–need areas, will be critical moving forward.

We identified four other findings that merit further investigation. First, ambiguous messaging about the relative value of ORS vs home–made sugar–salt solution can stifle ORS utilization. The definition of "oral rehydration therapy" changed four times within a decade [1], and may have had a lasting impact on clarity of communications about the gold standard for treatment of diarrhea. In Tanzania and India, both of which have a vibrant pharmaceutical market, the lack of focus on ORS messaging has allowed this product to be displaced by anti–diarrheals and antibiotics. In contrast, unambiguous messaging, that home–made sugar salt solution is not an adequate substitute for ORS, is critical for successful scale–up. Bangladesh switched from promotion of sugar–salt solution to promotion of ORS and the recent estimates suggest that ORS packets were used in nearly 80% of under–five diarrhea episodes in 2011. Second, rigorous commercial marketing approaches should be combined with effective interpersonal communication. An earlier case study of ORT success in Egypt highlighted the importance of utilizing scientific evidence with consumer and market research in crafting relevant and appropriate messages [8]. Commercial partners who truly understand marketing, and favor branded over generic marketing, can team up with groups providing interpersonal communication delivered in the home or through self–help groups. Third, it is clear that the market for diarrhea treatment products can be highly price sensitive (eg, pricing was a barrier in rural Madagascar). Thus partners must work to bring down prices in countries where they remain stubbornly high. Finally, support to the private sector needs to articulate a clear path towards the creation of a sustainable market. Subsidies for ORS may undermine sustainable markets, thus business models that encourage suppliers' reliance on external support risk being counter–productive in the long term. Few donor agencies recognize the importance of these domains of health services delivery to readily invest in them; public–private partnerships could lend support for this concept.

We found little information on the cost of scale–up efforts, primarily because this information has not historically been well–documented. We know that scale–up was done sustainably (and presumably affordably) in the five "successful" (>66% coverage) countries studied, and we have some anecdotal evidence from interviews and reports from major funders, but this is a gap in knowledge within the global community. To address this gap in future work, donors and governments would be wise to develop a rigorous monitoring and evaluation plan to track the impact of their investments and begin to improve our understanding of cost and sustainability.

There are several important limitations of this study. These case studies were initially conceived to inform programmatic decisions for the Bill & Melinda Gates Foundation; we recognize that the methods used did not emphasize repeatability as strongly as they would have done had our initial purpose been to publish these results in an academic journal. However, as important results came to light through this work, sharing the findings through academic means seemed appropriate. We therefore urge other researchers to look again at these and similar experiences with a view to obtaining further policy–relevant findings on factors leading to successful ORS scale–up.

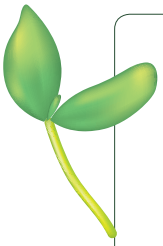
As previously noted, ORS coverage rates in the 1980s were available for few countries, but have since improved with MICS and DHS [1]. Although we identified data sources for ORS coverage in 96 countries, these periodic surveys, one–time field studies, supply chain data and national surveys rely on caregiver recall of the illness episode and any treatment sought and provided. We selected a subset of all countries that have attempted to scale up ORS and for whom data were available at the time; it would be of interest to repeat the studies, drawing from a wider selection of country experiences, and to validate the findings of our quantitative analysis by ensuring that more than one assessor scores the various country factors.

Finally, we relied on impressions from key informants, who undoubtedly had extensive knowledge of the historical contexts, the actors involved and the issues. We cannot rule out the potential reporting bias inherent in the role that the key informants or their organizations played in promoting ORS use. We did not maintain tape recorded interviews, as we suspected that key informants would not be as open to sharing their perceptions if they were being recorded. Although we developed one interview guide, given the semi–structured nature of the interviews interview questions were not completely standardized across countries.

## CONCLUSIONS

This study was an in–depth effort to objectively gather and compare the limited data available on the factors associated with successful and unsuccessful scale–up of ORS programs. We identified a number of characteristics of successful ORS scale–up programs, including involvement of a broad range of key players, addressing supply and demand

generation together, and working with both public and private sectors. Failure to involve key partners will often result in major gaps in the scale–up plan and critically affect sustainability. We found that the cost of scale–up efforts has not historically been well–documented. There are implications for the way that future ORS scale–up efforts should be directed to avoid some of the mistakes of the past. Efforts must synchronize demand generation, private provider outreach and public sector work. Rigorous monitoring and evaluation plans to track program impacts should be developed to address the gap in knowledge within the global community and improve our understanding of cost and sustainability. Future studies revealing lessons from other country experiences could also contribute to efforts to scale–up access to ORS and ultimately improve the lives of children who benefit the most from these efforts.



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**Competing interests:** All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 36 months; and no other relationships or activities that could appear to have influenced the submitted work; apart from that declared under Funding.

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# Survey of caregivers in Kenya to assess perceptions of zinc as a treatment for diarrhea in young children and adherence to recommended treatment behaviors

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**Background** In 2004, the United Nations Children's Fund (UNICEF) and the World Health Organization (WHO) revised their recommendations for management of acute diarrhea in children to include zinc treatment as well as oral rehydration solution (ORS). Little is known about how caregivers in low–resource settings perceive and use zinc treatment.

**Methods** Using a semi–structured quantitative survey, we interviewed Kenyan caregivers who had used zinc to treat children aged 6–60 months with an episode of diarrhea during the previous 6 months. The survey asked about experience using zinc, compliance with course and dosing regimens, and the attributes of zinc compared with other treatments. We surveyed a quota sample of 100 women from several communities where zinc treatment was available, primarily through public sector providers.

**Results** The mean duration of the reference diarrhea episode was 5.3 days (95% confidence interval (CI) 4.7–5.9). Eighty–two respondents had used zinc tablets, and 18 had given zinc syrup. Among those who used tablets, 62% reported giving zinc for fewer than the recommended 10 days, with a mean of 6.8 days (95% CI 6.1–7.4 days), and 50% said they had been instructed to give zinc for 5 days or less. Also, only 55% gave the correct daily dose. When asked about other treatments, 64% of the respondents reported using antibiotics, 59% ORS, and 56% a homemade remedy. Among the zinc tablet users, 55% provided zinc as the 3rd or 4th treatment for the reference episode. Also, 75% of respondents reported receiving the zinc treatment free of charge. Caregivers reported a very high level of satisfaction with zinc treatment, with 88% indicating that zinc (either in tablet or syrup form) was their most preferred treatment.

**Conclusions** Despite the potential benefits of zinc for children with acute diarrhea in low–resource settings, treatment regimens remain unwieldy and unrealistic, perhaps unnecessarily. Furthermore, the availability of zinc is limited primarily to public–sector providers. Increasing access to this treatment beyond the public clinic or hospital may accelerate uptake and sustained use.

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Globally, diarrhea remains one of the most significant causes of under–five mortality. It leads to an estimated 800 000 deaths annually in this age group, predominantly in developing countries [1]. In 2004, the World Health Organization (WHO) revised its recommendations for the man-

agement of acute diarrhea to include zinc treatment in conjunction with the administration of oral rehydration solution (ORS). Specifically, these guidelines recommend 20 mg of zinc per day at the onset of illness for 10 to 14 days (10 mg for infants under 6 months of age) [2]. These recommendations are based on evidence indicating that zinc can reduce the duration and severity of diarrhea and help to prevent recurrence for up to2 to 3 months [3]. In addition, some studies suggest that the promotion and use of zinc as a diarrhea treatment can reduce the inappropriate use of antibiotics [4].

Previous studies have indicated that caregivers sometimes use more than one intervention for treating diarrhea, and zinc has joined a number of interventions available to caregivers [5]. As with other interventions, zinc is not always used in isolation or just with ORS. Instead, it may be used in conjunction with one or more additional interventions. Some of these interventions, such as antibiotics and antimotility drugs, are not recommended for use in children in most cases. Others, such as home remedies, are valid components of oral rehydration therapy.

Because of the relatively recent addition of zinc to the portfolio of products for treating diarrhea in children, and the slow pace of uptake, there is limited information outside of controlled research settings on the behaviors of caregivers who have provided zinc to children, their ability to follow the therapy regimen, and their treatment preferences. Information from caregivers about how well zinc performs relative to other products, and their perceptions of the competing products, would be useful in developing programs aimed at increasing zinc use.

This article reports several key findings from a recent survey of caregivers in a rural area of Kenya about their behaviors and experience with using zinc to treat diarrhea in young children, their treatment and dosing practices, and views on how zinc compares with other interventions.

## METHODS

### Participants

We surveyed a quota sample of 100 caregivers in Kenya's Bungoma district. Interviewers visited households and administered a recruitment questionnaire to determine if they met the criteria for inclusion in the study. Key inclusion criteria included recent experience of diarrhea (within last six months), awareness of zinc and use of zinc in treating diarrhea in a child between 6 and 60 months old. We used a semi–structured oral survey with both open–ended and close–ended questions and interviewed caregivers in their homes. Because of the low coverage of zinc treatment in Kenya (as in most countries), survey participants were recruited from households with children in communities in Bungoma where this treatment was generally available through public or private health providers, clinics, and hospitals.

Participants were recruited in several villages (Sangalo, Kulisiru, Naitiri, Bungoma town, Kituni) within Bungoma district in Kenya's Western Province, a predominantly agricultural area. In these communities, blister packs of ten 20 mg tablets were generally available through public–sector clinics and hospitals as part of a pilot effort to introduce zinc for the treatment of diarrhea. Providers in these areas had received some training about new guidelines for diarrhea management that include use of zinc. In addition, a modest radio campaign in these areas had included information on both prevention of diarrhea (hand washing, sanitation, etc.) and treatment using ORS and zinc. Both the training and the media campaign had concluded approximately 18 months before the survey was conducted.

### Survey

An original survey was created for the purpose of this study. An initial draft was pilot tested for appropriateness and effectiveness, and to determine the usefulness and completeness of the responses. Based on the results of the pilot test the survey instrument was finalized. The implementation of the survey took approximately one hour to complete with most of the mothers.

The survey asked specifically about the most recent case of diarrhea in which zinc was administered. Survey questions elicited information pertaining to treatment practices, caregivers' overall satisfaction with use of zinc, comparisons with other products used, and understanding of the appropriate dosing regimen. To assist with recall and to overcome a respondent's potential inability to identify brand names of medicines or classifications, several areas of questioning relied on the use of pictures of locally available products (antibiotics, ORS, etc.). In all cases, the surveys were given in local languages.

### Data analysis and presentation

In the case of the categorical questions, frequencies have been reported. In the case of numeric questions, the full distributions of results, including mean, as well as median have been reported. Median has been reported where relevant in consideration of the sample and type of questions being analyzed. As the survey was designed to provide a snapshot of attitudes and behaviors within a relatively small sample, the emphasis was on identifying the typical patterns that emerge. Based on this, the median provides a good measure of typical behaviors in terms of actual number of days of episode or number of tablets given as opposed to the mean which provides the statistical average

but does not necessarily represent a typical behaviour.

The data were entered into computer and then analyzed using SPSS. Throughout the study, the market research agency (IPSOS Healthcare) maintained its standing permissions from the relevant authority in Kenya to conduct market and social research such as this study. IPSOS also adheres to the ICC/ESOMAR Code on the ethical conduct of market and social research [6]. This study was determined to be non–research by PATH's Research Ethics Committee. Individuals' participation in the surveys was entirely voluntary and anonymous, and all data was aggregated.

# RESULTS

## Respondent demographics

All surveyed caregivers were women who had used zinc to treat diarrhea in a child between 6 and 60 months within the past 6 months. **Table 1** summarizes the demographics of the participants. Approximately two–thirds were less than 30 years old. More than a half were working full or part time. Most came from the two lowest income groups, which is consistent with the rural, low–income status of the region.

**Table 1.** Percentage distribution of respondents by demographic characteristics

| Characteristic | % of respondents (n = 100) |
|---|---|
| Age: | |
| 18–24 y | 37 |
| 25–29 | 25 |
| 30–34 | 16 |
| 35 or more | 22 |
| Employment status: | |
| Not working | 41 |
| Working full time | 22 |
| Working part time | 29 |
| Unemployed, looking for work | 8 |
| Socio–economic grade:* | |
| C1 – Supervisory, clerical and junior managerial, administrative or professional | 13 |
| C2 – Skilled manual workers | 42 |
| D – Semi and unskilled manual workers | 45 |

*In Kenya, the socio–economic grades as initially defined by the British National Readership Survey (and often used in market research globally) were used with adapted criteria in common use among members of the Marketing and Social Research Association of Kenya [7].

## Duration of illness and treatments used

The mean duration of illness for which the caretaker provided zinc was 5.3 days (95% confidence interval (CI) 4.7–5.9), with approximately one–third of the cases lasting 6 days or more (**Table 2**). Ninety caregivers reported using at least two treatments, and 30 reported using at least four treatments in the reference episode (**Table 3**). Sixty–four reported using antibiotics for the same bout of illness, 59 used ORS sachets, and 56 used a home remedy. Forty–nine gave a home remedy as their first treatment. Among the 82 who administered zinc tablets, 19% administered the product as the 3rd treatment and 26% as the 4th treatment.

## Therapy regimen and dosing

The respondents were asked a series of questions about the zinc therapy and dosage regimen they had followed. Out of 82 zinc tablet users, 62% indicated that they had administered zinc for fewer than the recommended 10 days (mean = 6.8 days), 35% reported giving zinc for 10 days, and 2% administered zinc for 11 or 12 days (**Figure 1**). Among those who had given zinc for fewer than 10 days,

**Table 2.** Duration of reference diarrhea episode (zinc was typically started on day 3)

| No. of days | % of respondents (n = 100) |
|---|---|
| 1 | 5 |
| 2 | 5 |
| 3 | 11 |
| 4 | 25 |
| 5 | 20 |
| 6–10 | 28 |
| More than 10 | 6 |
| Median | 5 |
| Mean | 5.3 (95% CI 4.7–5.9) |

CI – confidence interval

**Table 3.** Number and sequence of treatments used in the reference episode of diarrhea (n = 100 respondents)*

| Treatment type | All treatments in reference episode† | First treatment used | Second treatment used | Third treatment used | Fourth treatment used |
|---|---|---|---|---|---|
| Homemade remedy | 56 | 49 | 4 | – | 1 |
| Powdered ORS | 59 | 13 | 26 | 8 | – |
| Zinc tablets | 82 | 7 | 29 | 19 | 26 |
| Zinc syrup | 18 | 5 | 7 | 4 | 2 |
| Antibiotics | 64 | 26 | 20 | 16 | 1 |
| Antimotility | 13 | – | 4 | 6 | – |

*Questions: When your child had this diarrhea episode, did you give anything shown on this illustration apart from anything you have already mentioned in relation to foods or diet? What did you use first? What did you use second? Third? Fourth?

†Some respondents indicated using more than four treatments. As a result, the sum of four treatments used may not total all treatments used.

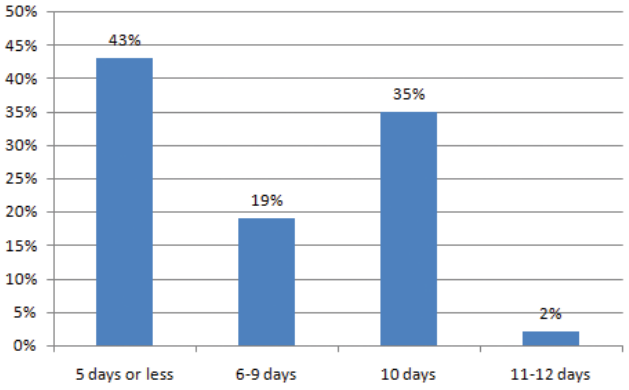



**Figure 1.** Duration of zinc therapy in days (n = 82 respondents).

4 in 10 reported that they had received instructions to administer zinc for 10 days but did not do so, and approximately 5 in 10 reported they had been instructed to provide zinc for 5 days or less.

Among the zinc tablet users, 13% reported giving less than the recommended daily dose (20 mg per day), 55% gave the correct daily dose, and 32% gave more than the recommended dose (**Figure 2**). Typically, those who under–dosed gave half a tablet per day and those who over–dosed gave one tablet twice per day.

## Source and cost

Among those who used zinc tablets, 92% reported accessing the product through a public source, either a government hospital (60%) or a government health center/clinic (32%) (**Table 4**). About 6% reported receiving the product from a private clinic or provider. In all instances, the number of tablets provided was 10, which is the total number of tablets in a blister pack typically available in Kenya. Among 18 respondents who used zinc syrup, most received the syrup from a public source. Only 9% of tablet users and 17% of syrup users reported paying for the product. Also, 75 respondents reported receiving ORS when they received the zinc.

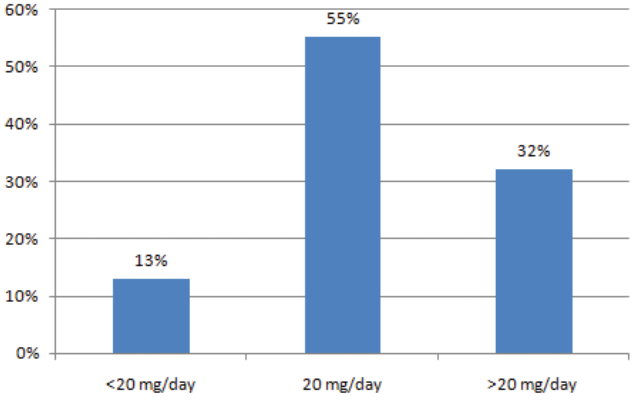



**Figure 2.** Daily dosage of zinc tablets (n = 82 respondents).

## Zinc treatment experience

Ninety–one women indicated that the zinc caused no negative effects on the child. Four, however, reported nausea, 3 reported dizziness, and 2 could not recall whether there were side effects. Despite minor, negative side effects in a few children, all 100 respondents said they would use zinc again the next time their child had diarrhea.

## Perceptions of zinc attributes

Most respondents had previously used other diarrhea treatments, with the most common being antibiotics, ORS, and home remedies (**Table 5**). Seventy respondents indicated that zinc tablets were their most preferred product, and 18 expressed a preference for zinc syrups. Although 91 respondents were aware of antibiotics and 82 had previously used them, only 5 indicated that antibiotics were their most preferred treatment.

Respondents who preferred zinc tablets over other products gave a number of reasons for this preference. About 74% reported that it "stopped the diarrhea," 60% said it "worked faster," and 40% said it "restores energy" (**Table 6**).

When asked what they believed zinc would do for their child based on their experience, 82% of caregivers first mentioned "stop the diarrhea" (**Table 7**). Attributes typically mentioned second were "improve the appearance of stools" (20%), "Help treat the diarrhea faster, so diarrhea did not last as long" (18%), and" reduce the frequency of bowel movements" (17%). Other commonly noted expectations included "improve child's energy level", "improve the child's appetite", and "give protection against future episodes of diarrhea."

## Discussion

In 2004, UNICEF and WHO introduced new guidelines for the management of acute diarrhea in children. The guidelines recommended use of zinc along with ORS because of the results of numerous clinical trials demonstrating that zinc treatment helps to reduce the duration and severity of illness and prevent early recurrence [2,3]. Zinc and ORS are not isolated in the marketplace, however. Caregivers and consumers have access to a range of products for treating diarrhea in children. Some are appropriate, and some are not. In addition, caregivers often use more than one product or intervention during a diarrheal episode. What has been poorly understood is how caregivers perceive zinc relative to other available interventions in ar-

**Table 4.** Source of zinc and median number of tablets provided

| Source | % of respondents using zinc tablets (n = 82) | Median number of zinc tablets provided | Mean number of zinc tablets provided (95% CI) | % of respondents using zinc syrup (n = 18) |
|---|---|---|---|---|
| Government health center or clinic | 32 | 10 | 7.98 (7.01–8.93) | 22 |
| Government hospital | 60 | 10 | 8.3 (7.56–9.04) | 61 |
| Private pharmacy | 1 | 10 | 10 | 6 |
| Private clinic | 5 | 10 | 10 | 6 |
| Other | 2 | n/a | | 6 |

CI – confidence interval

**Table 5.** Caregivers' awareness of and experience with various diarrhea treatments and their most preferred treatment (n = 100 respondents)

| Treatment | Aware of the treatment (%) | Ever used the treatment (%) | Most preferred treatment (%) |
|---|---|---|---|
| Antibiotics | 91 | 82 | 5 |
| ORS | 85 | 77 | 6 |
| Zinc tablets | 83 | 82 | 70 |
| Home remedy | 95 | 61 | 0 |
| Antimotility drugs | 49 | 19 | 1 |
| Zinc syrups | 28 | 22 | 18 |

ORS – oral rehydration solution

**Table 6.** Reasons for preferring zinc over other products

| Reason cited for preferring zinc | % respondents preferring zinc tablets (n = 70) | % respondents preferring zinc syrups (n = 18) |
|---|---|---|
| Effective – it stops diarrhea | 74 | 61 |
| It works faster | 60 | 50 |
| Restores energy | 40 | 39 |
| It helps the child gain appetite | 20 | 17 |
| Easily prepared/administered | 13 | 11 |
| It's cheap | 6 | 6 |
| Recommended by doctors | 6 | 11 |
| It's free of charge | 6 | 11 |

**Table 7.** Caregivers' expectations for zinc treatment based on experience (n = 100 respondents)

| Expectation about what zinc would do for child | 1st choice (%) | 2nd choice (%) | 3rd choice (%) | 4th choice (%) | 5th choice (%) |
|---|---|---|---|---|---|
| Stop the diarrhea | 82 | 9 | 1 | 1 | 0 |
| Reduce frequency of bowel movements | 9 | 17 | 7 | 1 | 0 |
| Help treat the diarrhea faster, so diarrhea did not last as long | 5 | 18 | 8 | 2 | 0 |
| Improve appearance of stools | 2 | 20 | 5 | 1 | 0 |
| Improve child's energy level | 0 | 8 | 10 | 3 | 1 |
| Improve child's appetite | 0 | 10 | 13 | 4 | 1 |
| Improve child's health | 0 | 3 | 5 | 6 | 2 |
| Improve look of child's eyes | 0 | 1 | 1 | – | 1 |
| Give protection against future episodes of diarrhea | 0 | 2 | 2 | 2 | 0 |
| Reduce vomiting or fever | 0 | 0 | 2 | 0 | 0 |

eas where caregiver preferences have not been significantly affected by introduction campaigns or pilot projects.

The survey reported in this paper provides indications of how zinc is perceived and the attributes ascribed to it by caregivers in a rural, low–resource setting. About half of the surveyed women reported that their first intervention was some kind of home remedy, which could include homemade sugar/salt solution, foods, liquids, or herbs. In addition, antibiotics were given as the first or second intervention by 46% of caregivers. For about one–half of the respondents, zinc was the third or fourth intervention introduced. This sequence of treatments may reflect access and availability. The ingredients for home remedies are usually readily accessible and do not require a visit to a provider, making it an easy first choice. Antibiotics are more widely available than zinc through private–sector providers, drug vendors, and some shops. During the survey, zinc tablets were generally only available from public sector medical providers, clinics, or hospitals, which tend to be less accessible.

Despite the heavy use of antibiotics, many of the caregivers expressed overwhelmingly positive views of zinc treatment. Eighty–eight percent indicated that zinc was their preferred intervention, and only 5% preferred antibiotics.

Of the 100 zinc users, 75 reported receiving ORS with the zinc. Of these, 59 actually used ORS during the course of the reference illness. Ideally, all 75 who received ORS should use it. However, the fact that some did not may reflect the lack of satisfaction with ORS as a treatment. Only 6% indicated ORS was their preferred treatment choice.

Consistent with previous studies, our survey results indicate that caregivers generally do not follow the recommended 10–day course of zinc treatment, even when they know they should do so [8]. Caregivers typically stop treatment once the child has returned to normal. Two–thirds of respondents reported giving zinc for fewer than 10 days. A large percentage indicated that they knew the correct regimen but for some reason chose to not follow it.

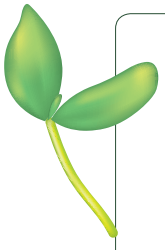
One–third indicated that they gave more than the recommended daily dose of one 20 mg tablet per day. Typically, those who gave more gave two tablets in a day. There may be an attitude of "more is better." In addition, given that most also gave antibiotics at some point, those who gave more than the daily dose of zinc may be mimicking a dosing regimen more familiar to them, one more similar to the regimen of antibiotics. Programs that promote zinc as an alternative to antibiotics and that seek to position zinc as a medicine may want to monitor dosing behaviors for appropriateness.

Recent studies suggest that 5–day course of zinc may be similar to a 10–day course in its effect on duration of illness [9]. Caregivers may be more likely to comply fully with the shorter course of treatment because it corresponds to the typical duration of illness and may reinforce satisfaction and confidence of self–efficacy. In addition, a 5–tablet pack would undoubtedly make the product much less expensive. More research is needed to assess the efficacy of a shorter course.

Previous studies in controlled settings have indicated that the introduction of zinc has been associated with decreased use of antibiotics [10]. The results of this survey suggest that zinc treatment has a very strong appeal among caregivers who have used it and is perceived as a highly efficacious product to stop diarrhea. More importantly, the vast majority indicated that they preferred zinc over any of the other options available to them, including antibiotics.

The small sample size and the quota sampling methodology need to be considered when evaluating the survey results. The survey was not intended to be representative of all caregivers. Instead, it provided a snapshot of current perceptions. The quota sample was used to allow for simplicity in locating and interviewing a population segment matching a specific criterion outside of a controlled research environment–namely, caregivers who had used zinc to treat diarrhea in the past 6 months. Because of the 6–month time frame, the survey is subject to recall bias. However, we believe the responses are predictive of future behaviors. In addition, knowing that the survey topic was about zinc may have biased the respondents towards a more positive perception of zinc. Finally, in most instances, respondents reported receiving the zinc treatment free of charge, which may have biased the stated preferences. We do not know how costs associated with obtaining the product would influence perceptions and behaviors.

The survey results suggest that zinc has the potential to supplant antibiotics as the diarrhea treatment of choice because of the strong perception that it stops diarrhea. However, treatment regimens for zinc remain unwieldy and unrealistic, perhaps unnecessarily. In addition, the availability of zinc is limited primarily to public–sector providers. Greater access and availability, beyond the public clinic or hospital, may accelerate uptake and sustained use. More research is needed to determine the preferences and perceptions of zinc when cost is a factor.



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# Global action plan for childhood diarrhoea: Developing research priorities

## Report from a Workshop of the Programme for Global Paediatric Research

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**Background** Childhood diarrhoea remains a major public health problem responsible for the deaths of approximately 800 000 children annually, worldwide. The present study was undertaken to further define research priorities for the prevention and treatment of diarrhoea in low and middle income countries. We used the Child Health and Nutrition Research Initiative (CHNRI) process for defining research priorities. This provided a transparent, systematic method of obtaining the opinions of experts regarding research priorities in childhood diarrhoea. The present report describes the deliberations of a workshop that reviewed these research priorities by stakeholders including colleagues from: government agencies, academic institutions, major funding agencies and non–governmental organizations.

**Methods** The workshop included 38 participants, divided into four groups to consider issues in the categories of description, delivery, development and discovery. Each group received 20 to 23 questions/research priorities previously identified by the CHNRI process. Deliberations and conclusions of each group were summarized in separate reports that were further discussed in a plenary session including all workshop participants.

**Results** The reports of the working groups emphasized the following five key points: 1) A common theme was the need to substantially increase the use of oral rehydration salts (ORS) and zinc in the prevention and treatment of diarrhoea. There is a need for better definitions of those factors that supported and interfered with the use of these agents; 2) There is an urgent need to determine the long–term effects of chronic and recurrent bouts of diarrhoea on the physical and intellectual development of affected children; 3) Improvements in water, sanitation and hygiene facilities are critical steps required to reduce the incidence and severity of childhood diarrhoea; 4)Risk factors enhancing the susceptibility and clinical response to diarrhoea were explored; implementation research of modifiable factors is urgently required; 5) More research is required to better understand the causes and pathophysiology of various forms of enteropathy and to define the methods and techniques necessary for their accurate study.

**Conclusions** The participants in this workshop determined that use of the CHNRI process had successfully defined those research priorities necessary for the study of childhood diarrhoea. The deliberations of the workshop brought these research priorities to the attention of stakeholders responsible for the implementation of the recommendations. It was concluded that the deliberations of the workshop positively supplemented the research priorities developed by the CHNRI process

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Childhood diarrhoea is a major public health problem globally. Despite major advances in prevention and treatment more than 800 000 children still die every year of diarrhoea [1]. In addition to the high burden of mortality, the effects of diarrhoea in children who survive are many, including stunting, neurodevelopmental delay, concomitant infections, recurrent diarrhoea and failure to thrive as well as other social and emotional problems. In response to this persistent burden of global illness, we initiated a global action plan for childhood diarrhoea ("D–GAP"). As part of the D–GAP plan we developed an approach to define focused research priorities aimed at improving the study and the care of children with diarrhoea globally. The technique used to define research priorities was developed by the Child Health and Nutrition Initiative (CHNRI) and is referred to as the CHNRI method [2]. Our use of this method of assigning research priorities is described in detail elsewhere [3]. It includes recommendations of research priorities of over 150 experts in childhood diarrhoea from around the world. The CHNRI process permitted us to determine the importance of these questions and to assign a ranking to them. Previous studies of childhood diarrhoea [4,5] used the CHNRI process to define research priorities to reach the Millennium Development Goals by 2015. The current study determines research priorities for the next 15 years. As a supplement to the CHNRI process, a workshop was held to discuss the results of the CHNRI process and to consider further those steps necessary to reduce the ongoing burden of childhood diarrhoea in the world.

This paper describes the results of that workshop held under the auspices of the Programme for Global Paediatric Research (PGPR). The goal of the workshop was to review the research priorities determined by the CHNRI process by stakeholders including academics, clinicians, and representatives of major funding agencies and non–governmental agencies.

## METHODS

The PGPR workshop was undertaken to consider the results of the CHNRI process and to comment on the recommendations therein. The workshop was held on May1, 2012, in Boston, Massachusetts, USA, during the annual meeting of Pediatric Academic Societies. The one–day event included 38 participants all of whom were "stakeholders" since they are involved in the care and study of children with diarrhoea. Participants included colleagues from: government agencies (National Institute of Child Health and Development, Center for Disease Control, Fogarty International, Canadian Institute of Health Research, and USAID), World Health Organization, paediatric associations (International Pediatric Association, American Academy of Pediatrics), non–governmental agencies (PATH, Management Science for Health, UNICEF, International Rescue Committee, Micronutrient Initiative) and several academic institutions in, Bangladesh, Canada, Nigeria, Pakistan, United Kingdom and United States.

The program began with two reviews for orientation. The first lecture delivered by Dr Zulfiqar Bhutta who described the overall global action plan for diarrhoea. This was followed by a presentation by Dr Alvin Zipursky who reviewed the CHNRI process and the results arising.

The participants in the workshop formed four working groups, Discovery (New interventions), Description (Epidemiology), Development (Improving existing interventions) and Delivery (Health policy systems, including cost–effectiveness). These four groups were defined using the criteria previously described by Rudan et al [2].

Each group was given the top 20–23 questions (research recommendations) from their corresponding categories, identified by the CHNRI process (**Tables 1 to 4**). The groups were asked to review their list of research questions and consider issues raised by those questions. Following the deliberations of each group a report was prepared and presented in a plenary session of all workshop participants. Participants were invited to discuss the reports and issues raised. Following the workshop the group chairs were asked to prepare final reports which are considered in this article. The four groups were asked to consider the following when discussing each of their 20–23 recommendations:

- What is the relative importance of each recommendation?
- What steps are required for implementation of each recommendation?
- Clarify the phrasing of each question/recommendation to improve implementation
- Provide suggestions of groups or individuals who could implement specific recommendations.
- How can global resources collaborate to implement specific recommendations?
- What should be the long term goals of D–GAP to insure implementation of the recommendations?
- Comment on the CHNRI process as a means of determining research priorities in the development of a global action plan for childhood diarrhoea.

## RESULTS

### The Discovery Group

This group analyzed the 23 questions listed in **Table 1** and recognized that they represented issues that could be presented to major funding agencies. The first area identified

**Table 1.** Discovery related questions identified by the CHNRI process

| | |
|---|---|
| 1 | How do we improve the efficacy of live oral vaccines against gut or gut–acquired pathogens in low– and middle–income countries? |
| 2 | Develop successful vaccine against *Cryptosporidium*, *Shigella*, *Giardia*. |
| 3 | Research suggests that cognitive deficits associated with early childhood diarrhoea persist for at least 4 or 5 y. What measures can capture this deficit? How long does this deficit persist? |
| 4 | What are the fully burdened cost–benefits of different diagnostic technologies – molecular vs culture vs antigen detection vs microscopy? |
| 5 | What is the role of short–chain fatty acid delivery to the colon in enhancing sodium and water absorption, reducing fluid secretion and facilitating mucosal repair? |
| 6 | By what mechanisms (at gut and immunologic level) do malnutrition and various micronutrient deficiencies increase risk of severe diarrhoea? |
| 7 | Identify and validate biomarkers of "gut health" (eg, gut barrier function, inflammatory biomarkers, etc.) to identify those children at risk of chronic enteropathy. |
| 8 | What is the role of vitamin D deficiency in diarrhoea risk? |
| 9 | Study the effect of zinc on the gut secretory mechanisms. |
| 10 | What is the role of co–infections in childhood diarrhoea? |
| 11 | Can a water storage vehicle be developed with slow release halogen? |
| 12 | Can and should cheap and rapid diagnostic tests for common enteric pathogens be created for use in the field? |
| 13 | Will field or clinical use of rapid diagnostic tests for common enteric infections lead to improved accuracy of disease diagnosis (and more appropriately, targeted therapies or health measures)? |
| 14 | Will more rapid and accurate diagnosis of enteric diseases (and use of targeted therapies) improve measures of disease outcome and long–term health? |
| 15 | Will targeted therapies and new diagnostics decrease antibiotic resistance? |
| 16 | What is the effect of enteral glutamine on mucosal and systemic immune responses in children with diarrhoea? |
| 17 | Assess the utility of targeting NKCC, K channels and Na–coupled transporters in diarrhoea therapy. |
| 18 | What is the better approach to improve the intestinal microbiome in order to enrich the nutrient absorption and protect the intestinal barrier function following enteric infections? |
| 19 | Are there enteropathogens (particularly chronic infections for which treatment exists, ie, helminths) that modulate the incidence and severity of other enteropathogens? |
| 20 | Although mucosal immune responses are elicited by oral vaccines, responses to such vaccines may be relatively short duration compared to that induced by wild type disease. What are the reasons for this? What are the mediators and modifiers of long–term mucosal immunity? Would improved vaccines, regimens and/or immunization strategies result in longer duration? *V. cholerae* is a well studied, paradigmatic, non–invasive pathogen, and oral and live attenuated cholera vaccines, as well as subunit and conjugate vaccines exist. Could cholera be used as a mucosal model to address these questions? Such an approach may not only inform how to induce long–term immunity against mucosal pathogens as a group, but, if successful, could facilitate roll out and implementation of current or improved cholera vaccines. |
| 21 | Develop molecular techniques for understanding co–infections (bacterial and parasitic and viral causative agents). |
| 22 | How do age, aetiology and severity of diarrhoea affect the integrity of the gut and subsequent growth/health? |
| 23 | Establish the role of chloride channels in rotavirus–induced diarrhoea and then develop and test inhibitors of calcium activated chloride channels. |

CHNRI – Child Health and Nutrition Research Initiative, KNCC – Na–K–Cl transporter

was an improved understanding of mucosal defence mechanisms. This is a fundamental research initiative concerning the regulation of innate and adaptive immune responses at the gut level and improved characterization of those factors that influence that response such as the microbiome and certain pathogens. A second major area worthy of additional research funding is the mechanism underlying enteropathy, including the effects of nutrition and the gut microbiome on intestinal function as well as repair of the bowel following either repeated bouts of acute diarrhoea or chronic enteropathy. The group also recognized the need for research in terms of the impact of enteric infections on long–term brain development, physical growth and metabolic consequences.

The group emphasized the need for improved diagnostics and technology to further the understanding of bowel function. This could include studies of intestinal motility as well as nutrient and fluid losses. In addition the Discovery Group identified a need for effective long–term studies of child health including weight and anthropometry as well as nutritional status and indices of child development. The development of biotechnology devices for specific markers of water quality, sanitation and food safety were also identified as research priorities.

## The Description Group

This group received 20 questions for appraisal (**Table 2**). They first considered recommendations regarding risk factors and elaborated on them for appraisal. For instance it was noted that sickle cell disease, which is very common in many low income countries could well be an important determinant of the severity of diarrhoea and resulting morbidity and mortality. Implementation of these issues was discussed ; it was felt that determining genetic risk factors such as sickle cell disease would be feasible either with a case–control or prospective study design. Nutritional risk factors could be examined through the new birth cohort studies. This group felt that data on the effect of HIV on diarrhoea are likely available now.

The importance of breast–feeding was recognized however it was felt that the focus for further studies should be on behavioural changes to increase breast–feeding rather than simply describing the effect of breast–feeding on diarrhoeal disease, for which there is ample evidence. Concerning recommendations on the aetiology of diarrhoea this group felt that current ongoing studies would likely provide sufficient information at this point.

This group then discussed the need for indicators to measure treatment practices and decided that this was a very

**Table 2.** Description related questions identified by the CHNRI process

| | |
|---|---|
| 1 | What are the barriers against the appropriate use of ORT? |
| 2 | What factors have led to the decline in ORS use rates in countries where rates were high and now are low? |
| 3 | What are the attributes of successful and sustainable childhood diarrhoea programs? E.g. what have been the design and strategies used in programs and interventions where the burden of diarrhoeal diseases has been drastically reduced? |
| 4 | To what extent does the roll out of rotavirus vaccination reduce the burden of acute dehydration as well as all diarrhoeas? |
| 5 | What are the individual risk effects of malnutrition, poor sanitation, low level of education and reduced levels of vitamins and micronutrients in acquiring diarrhoea in children living in the developing world? |
| 6 | What are the developmental stages/ages at which children are most at risk of long–term cognitive impacts from diarrhoea? Is there a critical window for early childhood diarrhoea that can affect future physical and mental development (0–6 mo, 6 months – 2 years or 3–5 years)? (If it is greatest in the first six months to one year, one might place more emphasis on breast feeding and weaning practices) |
| 7 | Evaluate if early initiation and exclusive breastfeeding is associated with reduced burden of diarrhoea and improved growth. |
| 8 | Do access to, and benefits received, from nutritional supplementation programmes reduce global burden of diarrhoeal disease? |
| 9 | What are the risk factors for diarrhoea mortality? |
| 10 | What is the role of host factors in determining diarrhoea morbidity and mortality (eg, demographic, nutritional, genetic)? |
| 11 | What are the key transmission pathways and dominant pathogens of DD in different settings? |
| 12 | What is the sensitivity and specificity of the current home oral rehydration treatment and ORS questions in DHS and MICS and are there better questions to measure use of ORS? |
| 13 | What micronutrient deficiencies are risk factors for diarrhoea incidence or severity? |
| 14 | How does childhood diarrhoeal illness correlate with adult height? What is the impact of acute, prolonged, persistent and recurrent diarrhoea on growth trajectories of children in impoverished endemic areas? |
| 15 | What are the environmental and social/behavioural risk factors for diarrhoea? |
| 16 | What is the best current estimate of child mortality from diarrhoea globally and in various regions of the world? |
| 17 | Which pathogen is the most important cause of diarrhoea in target ages, seasons and regions? |
| 18 | What are the major bacterial, viral and parasitic pathogens responsible for mortality/morbidity in acute and chronic diarrhoea among children worldwide? Are there global monitoring systems? |
| 19 | How can we utilize data collected on childhood diarrhoea diseases to reduce rates of infection and disease? Can this data be used to help target the development of specific vaccines, or will vaccines actually be applicable? On the other hand, can these data be used to target areas for improved hygiene/sanitation to reduce incidence? |
| 20 | Develop and test and ordering algorithm for health worker/community workers/physicians for identifying causative agents of diarrhoea in an individual or outbreak situation (diagnostic test algorithm). |

CHNRI – Child Health and Nutrition Research Initiative, ORS – oral rehydration salts, ORT – oral rehydration therapy

high priority. The group also discussed various barriers and incentives for treatment provision. These included financial and household barriers, as well as equity issues including gender.

It was suggested that it would be important to determine the clinical characteristics of fatal cases in acute and persistent diarrhoea. Verbal autopsies were suggested as a means to understand the nature of fatal diarrhoea . This group also identified a need for studies of why diarrhoea mortality has declined worldwide. For example, data should be available in studies in Brazil where there has been a substantial drop in diarrhoea mortality [6]. Furthermore, it was suggested that there is a critical need for data on country specific diarrhoea mortality, incidence and severity.

## The Development Group

The Development Group divided the 21 assigned research questions (**Table 3**) into several categories and discussed the importance of the research questions. Under the category of food and nutrition, members of the group assigned high priority to the question of the effects of zinc supplementation on diarrhoea prevention as well as determining whether iron and other micronutrient supplements might impact the absorption or bioavailability of zinc. The group assigned a lower priority to determining which practices are most efficacious in improving the safety of food served to children 0 to 59 months at home.

In the category of education, the highest priority was assigned to the question of whether the provision of low cost sustainable health education packages through community involvement to caretakers could serve to prevent diarrhoea and impact children's long–term cognition and school achievement. Assigned a lower priority was the question of whether trained groups within a community could improve infant and child nutrition and reduce diarrhoea through update of preventive and therapeutic strategies.

In the category of treatment this group assigned the highest priority to three questions:

1. Can an appropriate mixture of zinc – ORS be developed such that a sufficient dose is received by the child to reduce duration and stool output?
2. Could an ORS formula be developed that decreases stool output as well as improving hydration?
3. Does calcium–supplemented ORS reduce fluid loss?

Of lower priority was the question of whether zinc supplementation could be used as an adjunct to standard treatment of acute bloody diarrhoea.

**Table 3.** Development related questions identified by the CHNRI process

| | |
|---|---|
| 1 | How do we improve the availability and uptake of interventions for diarrhoea that have consistently been shown to be effective (eg, the 2009 WHO 7–point plan)?<br>Can a mixture of zinc and ORS be developed that successfully reduces duration and stool output? |
| 2 | Do interventions to support mothers (eg, reduce maternal depression, strengthen maternal coping, problem solving for child health) impact diarrhoeal disease outcomes? Provision of low cost/sustainable health education packages through community involvement (community motivation steps) to mothers to prevent diarrhoea and assess effects on children's cognition and school achievement. |
| 3 | What is the impact of waterless hand sanitizer use on diarrhoea risk in household and school setting, particularly in water–constrained areas? |
| 4 | What are the critical times to wash hands to reduce diarrhoeal disease? |
| 5 | Could an ORS formula be developed that decreases output? |
| 6 | Evaluate calcium–supplemented ORS to reduce fluid secretion through enterocyte calcium receptors. |
| 7 | How might HWTS demonstration at ORT corners increase uptake and use of HWTS products and subsequent reduction of diarrhoeal disease incidence in mothers presenting with infant at ORT corners? |
| 8 | What is the best way to improve the microbial quality of the food served to children 0–72 months at home? |
| 9 | Assess the efficacy of zinc supplementation as adjunct to standard anti–*Shigella* treatment on the gut mucosal and systemic response. |
| 10 | What is the impact of intermittent water supply on DD and how can we ensure the microbiological quality of intermittent piped supply? |
| 11 | Develop age–appropriate, geography–appropriate, duration–appropriate (acute/chronic), and characteristic–appropriate (bloody/non–bloody) algorithms for management of different diarrhoea syndromes in different paediatric hosts. |
| 12 | What is the effect of intermittent therapy with zinc on diarrhoea prevention when given at routine contacts? |
| 13 | What are the triggers of handwashing behaviour change at different occasions and for different target groups (eg, parents, adolescents)? |
| 14 | What effect does the provision of sanitation and water supply in schools have on community behaviours with respect to sanitation and hygiene and what are the health outcomes for children in school and for the wider community? |
| 15 | What is the potential for women's groups or peer–counselling/training of community–based cadres to improve infant/child nutrition and reduce diarrhoea through the update of preventive/therapeutic strategies? |
| 16 | Determine whether iron and other micronutrient supplements reduce the effectiveness of zinc to prevent diarrhoeal disease (RCTs). |
| 17 | In randomized controlled field trials in Sub–Saharan Africa and South and Southeast Asia, oral rotavirus vaccines have conferred ~50–60% efficacy. WHO SAGE has recommended their use and GAVI has committed to finance introduction of rotavirus vaccine into national EPIs. If a poor Sub–Saharan African country achieves a high coverage of rotavirus vaccine, is it conceivable that the indirect protective effects, in addition to the direct protection, may result in a greater than expected impact on diminishing disease burden? Should it be a high priority to affirm (or disprove) this hypothesis since it has important public health implications? |
| 18 | In view of clear reduced immunogenicity of oral enteric vaccines in children in developing countries, should significant resources be allocated to better understand the reason for such findings and for development of alternative modes of delivery (modified oral delivery and/or alternative routes) for efficient immunization with enteric vaccines in these populations? |
| 19 | There are two licensed non–living oral cholera vaccines that require two doses to immunize and are useful for control of endemic disease. For control of epidemic cholera, particularly in unsettled and emergency situations, should resources be applied to complete development and achieve licensure of one or more single–dose oral cholera vaccines? |
| 20 | Natural *Shigella* infection confers around 70–75% protection against the homologous serotype for a limited period of time (~2–3 years). This figure parallels the level of serum and antibody secreting cell (ASC) responses to natural infection. What would be a priority for investment of research resources: development of multicomponent (5–valent) vaccines, which will cover the most common serotypes reaching this extent of protective efficacy in developing countries? And/or (?) discovery of common protein antigens (perhaps secreted proteins in vivo) which will cross–react with *Shigella* homologous and heterologous sera and further study their immunogenicity and potential to cross protect? |
| 21 | Natural enterotoxinogenic *Escherichia coli* (ETEC) infection confers around 70–75% protection against the homologous strain for a limited period of time (~2–3 y). This figure parallels the level of serum and antibody secreting cell (ASC) responses to natural infection. What would be a priority for investment of research resources: development of multicomponent (eg, multivalent colonization factor antigen–based) vaccines, which will cover the most common antigenic types reaching this extent of protective efficacy in developing countries? And/or (?) the discovery of common protein antigens (perhaps secreted proteins expressed in vivo) which will cross–react with ETEC homologous and heterologous sera and further study their immunogenicity and potential to cross protect? |

CHNRI – Child Health and Nutrition Research Initiative, EPI – Expanded Programme on Immunization, HWTS – household water treatment and storage, ORS – oral rehydration salts, ORT – oral rehydration therapy, RCT – randomised controlled trials, WHO SAGE – World Health Organization Strategic Advisory Group of Experts (SAGE) on Immunization

## The Delivery Group

This group divided the 22 questions (**Table 4**) into four major themes.

1. The use of behavior modification and communication strategies in the home and in the community

This group examined the drivers of prevention and barriers to treatment for reducing childhood enteric disease. The group determined that there is need for research to determine the most effective behavioural changes and communication strategies to increase utilization of treatment such as oral rehydration solution and zinc. Research questions in this group also addressed the behavioural changes in communication strategies necessary to promote important prevention strategies such as handwashing with soap, household water treatment, sanitation and nutrition. It was recognized that all of these included drivers and barriers such as poverty, physical inaccessibility, maternal education and cultural practices. This group also considered communication strategies such as household marketing, mass communication and social marketing.

2. The delivery of the products, including the role of health care workers, the available facilities and training

This group considered delivery of adequate health worker training as well as promotion of prevention and treatment

**Table 4.** Delivery–related questions identified by the CHNRI process

| | |
|---|---|
| 1 | Identify and test alternative delivery strategies designed to ensure that ORS and zinc are reaching hard to reach populations and being used by the poorest of the poor (for example, home distribution of ORS and zinc). |
| 2 | What factors drive care–seeking behaviour during a childhood diarrhoea disease? How can we position ORS and zinc to best respond to these factors? |
| 3 | What factors most effectively drive caregiver demand for ORS and zinc? |
| 4 | What is the added impact of integrated community case management on early and equitable administration of appropriate treatment for acute diarrhoea? |
| 5 | Determine how the perception of diarrhoea as an illness affects:<br>Key household practices like handwashing;<br>Willingness to pay for point of use water disinfection products;<br>Care seeking; and,<br>Compliance to ORS and zinc treatment. |
| 6 | Determine how best to move caregivers from knowledge of ORS and/or zinc treatment to actual trial and eventual adoption as routine practice. Identify the stages of behaviour change in order to tailor messages accordingly. |
| 7 | Do we need to move from general and generic to more specific targeted messaging? When and what would this include? |
| 8 | To move a caregiver from awareness to trial of ORS and zinc, what will be the relative impact of mass media vs group vs one–on–one communication strategies?<br><br>Does this vary by whether a rural or urban population? |
| 9 | What contextual or cultural factors positively or negatively influence ORS and zinc utilization or compliance? |
| 10 | Determine the best indicators for measuring the effectiveness of communication messages for childhood diarrhoea and the effectiveness of different communication channels in terms of a) awareness b) readiness to try, and c) actual use of ORS and/or zinc |
| 11 | Does the community–led total sanitation approach lead to decreased diarrhoea risk? |
| 12 | How best to effectively reduce the gap between knowledge and use of simple and effective interventions, such as ORS (eg, behavioural research, product improvements)? |
| 13 | What is the effect of promoting a strategy asking mothers to keep ORS packets and zinc at home for use in case of diarrhoea on use and coverage, when compared to the usual strategy that requires mothers to go to a CHW or a Health Facility to obtain ORS and zinc in case of diarrhoea? |
| 14 | Test indicators to determine effectiveness of IMCI and iCCM in reducing the burden of childhood diarrhoea. |
| 15 | Are ORT corners effective in reducing hospital admissions for severe to moderate dehydration? |
| 16 | What are the costs and benefits of the education measures to decrease diarrhoeal disease in the developing world? |
| 17 | Conduct social marketing research to improve acceptability of zinc treatment in the public and private sections – packaging, language, health messages. |
| 18 | Which strategies and messages are effective in convincing health care providers of the advantage of ORS and zinc compared to antibiotics or other drugs? |
| 19 | What factors, including mothers' education, would influence acceptability of zinc supplementation and high/earlier use of ORS in the community? |
| 20 | What is the effectiveness of iCCM in increasing coverage of zinc and ORS? |
| 21 | Assess effectiveness of delivery strategies to provide zinc and ORS |
| 22 | Assessment of key knowledge gaps in community awareness of the relationship between nutrition and the occurrence of diarrhoea and the relationship between diarrhoea and long–term development in children. |

CHNRI – Child Health and Nutrition Research Initiative, iCCM – Integrated Community Case Management, IMCI – Integrated Management of Childhood Illnesses, ORS – oral rehydration salts

strategies. Their recommendations consisted of various communication strategies, including marketing at the household level, mass communication and social marketing to promote health

3. Product improvements by both the private and public sectors

The Delivery Group found a need to evaluate innovative strategies to improve the acceptability palatability and positioning of ORS and zinc products. Members also determined that there is a need to monitor and evaluate new products, evaluate communication methods (packaging, language and health measures) and deliver these products effectively, through various pathways including private–public partnerships.

4. The cost of the products

Issues considered included an appraisal of how much are consumers in low and middle income countries willing to pay for zinc, ORS, water disinfection products, sanitation, rotavirus and measles vaccines?

Several questions, in addition to those that had been submitted, were added: What are the key knowledge gaps in community awareness of the relationship between nutrition and the occurrence of diarrhoea and the relationship between diarrhoea and long–term development in children? What are the appropriate tools to encourage appropriate use of antibiotics to treat the diarrhoea of childhood? What are the costs and benefits of the education measures, for both consumers and health care workers to decrease diarrhoeal disease in developing countries?

Also discussed were strategies to ensure that ORS and zinc as well as handwashing, household water treatment, nutrition, sanitation and vaccines are reaching hard–to–reach populations with emphasis on the poor. The group suggested that this would include the impact of Integrated

Management of Childhood Illnesses (IMCI) for the appropriate treatment for acute diarrhoea. Other suggestions included oral rehydration therapy (ORT) corners, social marketing, commercial outlets, pharmacies, faith–based organizations, in addition to identifying the need to reduce cost barriers

## DISCUSSION

This report describes a workshop in which research priorities determined by the CHNRI process were then evaluated by a group of stakeholders. The CHNRI process provided a systematic, transparent method of obtaining and tabulating the opinions of experts regarding research priorities in childhood diarrhoea.

Kosek at al [5] note that the use of the CHNRI technique minimizes personal biases, however they state further: "there is a possibility that a different group, composed of many policymakers and program officers rather than the group that performed this exercise may yield somewhat different results". Others have also commented on the need to include the opinion of stakeholders in an evaluation of the research priorities of the CHNRI process [7].

This workshop included participants involved in global child health who were able to consider proposed research priorities in relation to their own programs and experience. Furthermore the workshop provided an opportunity to consider the issues associated with implementation of the recommendations. Finally the workshop brought research priority issues to the attention of the participants, an important learning experience for those responsible for designing, implementing and funding programs aimed at reducing the global burden of childhood diarrhoea.

The deliberations and recommendations described in the Results section provide suggestions regarding priorities, related factors, additional recommendations and issues to be considered regarding implementation. It is evident that a major priority is the effective implementation of the use of ORS and zinc therapy. The Delivery Group discussed, in detail, the many issues that have to be considered to achieve optimal use of these agents including the importance of education as well as training both in the homes and in the community. Their recommendations constituted a veritable "plan for action" to ensure that this therapy reaches all those who require it.

It was recognized by several of the groups that the major concern internationally has been the high mortality of childhood diarrhoea. Noting the substantial reduction in diarrhoea mortality over the past decades, several groups emphasized the importance of also considering the long–term effects of diarrhoea in low and middle income countries, including malnutrition, physical and cognitive development as well as recurrent and chronic diarrhoea.

The Discovery Group recognized that many of the research priorities recommended by the CHNRI study relate to basic research and could be included in several major categories of research activities supported by national and international funding agencies. Furthermore this group described and emphasized the need for new technology to support the required basic and applied research.

The Description Group discussed the importance of risk factors significant in diarrhoeal mortality. For example, sickle cell disease, a common condition in Africa and India, can be a major factor in contributing to the lethal effects of diarrhoea. The group then recommended how this and other risk factors could be studied. This group also recognized the potential of learning more about the causes of death from diarrhoea by detailed studies of children who had died, including the use of verbal autopsies. It was also suggested that a study should be undertaken to determine the reasons for the recent reduction of diarrhoeal mortality worldwide.

Several groups discussed the importance of improving sanitation and water supply. In the plenary session there was agreement and emphasis of this as a most important topic, although it is a topic that has not had the general acceptance and priorities that it deserves.

All participants judged that the CHNRI process had successfully identified research priorities necessary for the study of childhood diarrhoea. The workshop contributed to the recommendations of research priorities provided by the CHNRI process in the following ways:

It clarified the phrasing of questions, a necessary step to further their eventual implementation.

It defined steps necessary for implementation of specific recommendations.

It brought the questions to the attention of stakeholders who are responsible for the implementation of such recommendations.

It provided an opportunity to discuss factors related to the individual questions: factors that have to be considered in the understanding of the recommendations for their eventual implementation.

Appreciation of the epidemiological issues related to an understanding of the global problem of childhood diarrhoea.

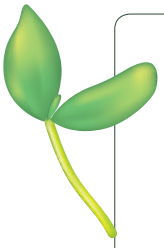
The inclusion of the recommendations of the workshop in the PGPR website permits ongoing discussion, recommendations and criticisms necessary for the continuing development of the research priorities necessary to solve the problem of childhood diarrhoea. The final complete reports of all workshop groups including a

list of all participants can be found on the web site of the Programme for Global Paediatric Research (www.globalpaediatricresearch.com).

## CONCLUSION

The global action plan for diarrhoea required a means of determining research priorities for the future. The CHNRI process provided an objective and transparent method of providing these priorities. The workshop, described herein, provided input from stakeholders who are responsible for the implementation and evaluation of clinical and research programs aimed at reducing the global burden of childhood diarrhoea. Not only did the workshop serve to inform this group of research priorities but it also provided these individuals with further information on research priorities including avenues for funding and steps necessary for implementation.

The combination of the CHNRI process with input of stakeholders provides both a comprehensive education process and an in–depth discussion of the many issues involved in the implementation of research priorities to reduce the global problem of childhood diarrhoea.



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**Competing interests:** All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf. The authors declare no financial conflict of interest or other relationships or activities that could appear to have influenced the submitted work.

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# Guidelines for Authors: Editorial Policy and Manuscript Preparation

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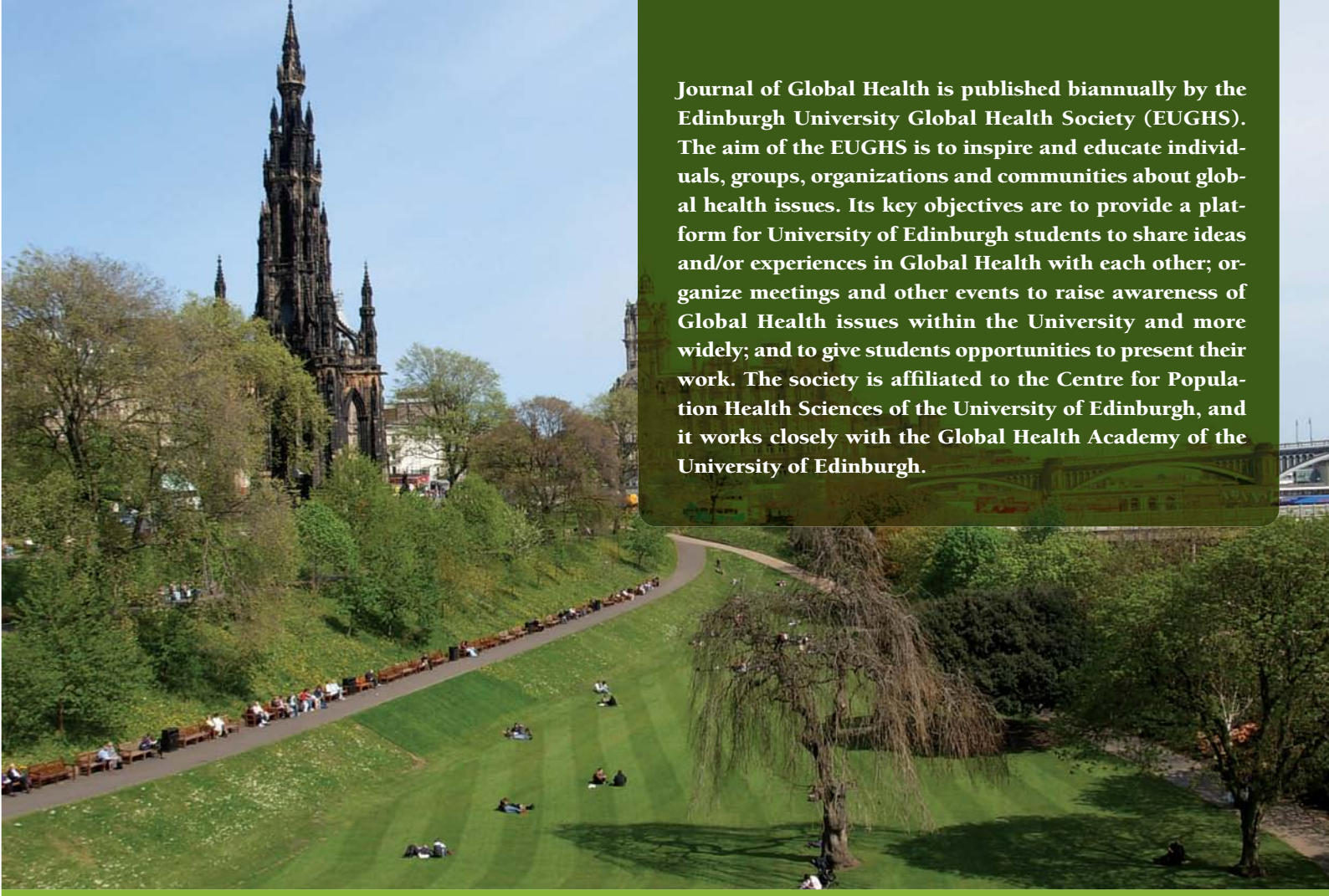

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