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Cleanliness champions: Village children learning the basics of hand hygiene in Baray, Cambodia. Photo by Luke Chan, EUGHS member.

Journal of Global Health: The Mission Statement

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

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

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

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

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

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

March 7, 2011

The Editors, Journal of Global Health

Respiratory syncytial virus (RSV) disease – new data needed to guide future policy

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RSV is the main cause of childhood lower respiratory infections, globally, an important cause of childhood wheeze and may be responsible for a substantial burden of disease in the very elderly and in adults with chronic medical problems, such as COPD. It is thus responsible for substantial healthcare and social costs. There are currently many companies and academic groups developing and testing candidate vaccines and there is an expectation that these will lead to effective and safe vaccines which will be available to health systems globally in the short – medium term. Despite this, there is an incomplete understanding of RSV disease, especially in adult groups, and large scale data are only available from a few countries and settings leading to low levels of awareness of the importance of this pathogen. We discuss the need for widespread national sentinel systems of RSV surveillance and some means by which this could be achieved. These data will be needed by national policy makers and immunisation advisory groups to guide future priority setting and decision making.

n this issue of the Journal of Global Health there is a short series of papers on respiratory syncytial virus in-L fection (RSV). RSV is a major cause of morbidity and mortality worldwide and has been estimated to cause about 34 million episodes of acute lower respiratory infections (ALRI) in young children globally each year, with over 3 million severe enough to cause hospitalisation [1]. These episodes are followed by an increased risk of wheeze in later childhood. In addition, the role of RSV in causing disease in adults with chronic medical problems and in the very elderly is ill-defined but may also represent a substantial burden of disease. Reports from Falsey in the USA and a recent study from UK suggest that RSV may be an important cause of primary care consultations, hospital admissions and deaths from cardiopulmonary causes following RSV infection in these adult risk groups, similar to influenza [2].

In 2015, the World Health Organization (WHO) Product Development for Vaccines Advisory Committee (PDVAC), which scans the horizon for likely important vaccine developments in the coming decade, highlighted RSV as "a pathogen for which there is major vaccine pipeline activity, high technical feasibility, and major disease burden in low and middle income countries (LMICs)". They summarised the current status of vaccine research as of June 2014 [3], and this status is updated by PATH in their RSV vaccine snapshot graphic [4]. A number of different vaccine candidates are being developed and tested in phase 1–3 trials and there is an expectation, echoed by WHO PDVAC that these may become available to health systems in the short – medium term.

Currently, these developments are gaining momentum ahead of action to gather information to raise awareness and inform policy discussions globally. Although RSV dis-

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ease accounts for very significant health care and social costs globally, there is a low level of recognition of this among government policy makers. Thus, to support these developments there is a need to assemble epidemiological data on RSV through national and other large scale surveil-lance systems. This could provide data on:

- burden of RSV disease by age group, by key risk groups and by geographical setting;
- RSV seasonality patterns across the world; and
- RSV viral parameters such as subtypes and genotypes.

They could also provide baseline data on hospitalisations from RSV ALRI against which the impact of a future vaccine could be assessed at national scale.

RSV is not currently a notifiable disease and there are no well-established ongoing surveillance systems in existence. A sophisticated Global Influenza Surveillance and Reporting System (GISRS) functions well with data from over 140 National Influenza Centres globally and with the sharing of over 1 million respiratory samples for influenza detection. The paper by Shi and colleagues in this edition of Journal of Global Health demonstrates that about 90% of ALRIs in children in which RSV is detected can be causally ascribed to RSV. Some of the GISRS sites conduct acute surveillance of Severe Acute Respiratory Infections (SARI) in all age groups and although case definitions and sampling procedures are designed to identify episodes of SARI due to influenza there is the potential to adapt this surveillance system to also identify episodes of ALRI due to RSV. Key issues to address in this adaptation would include the differing seasonal pattern of RSV, the different age pattern of RSV disease (with more emphasis on the first 2 years of life) and the differing clinical presentation of cases (with fever absent in up to 80% of cases in children) [5]. Most severe cases of RSV infection, including RSV-related deaths, occur during the first months of life, during which fever is often absent and apnoea may be the presenting or even only symptom, similar to pertussis. These represent major challenges to overcome if a parallel system for RSV within GISRS is to be developed. However, this approach perhaps represents the only feasible means by which most LMICs will be able to generate substantial amounts of structured and reasonably representative RSV data which can be used to inform decision making on the priority for future RSV vaccine introduction. These systems will under-estimate true RSV disease burden (due to some children with RSV disease not attending for care in LMIC) but establishing such a surveillance system would represent a quantum leap forward in the availability of health care data on RSV and in data on RSV seasonality from most countries globally.

It is not fully clear how the existing GISRS systems can best be adapted for RSV surveillance but this will at least require the development of separate case definitions and RSV-specific standard operating procedures for identification of the target population, data collection, analysis and reporting. This will require specific study and the new scheme will need to be validated before wide adoption. The proposed global web-based FLuMART platform for sharing epidemiological (FLuID) and virological (FluNet) data could serve as a base from which an RSV information and reporting system could be built. A major advantage of this approach would be the existing excellent linkages to national policy makers globally who already receive weekly reports from GISRS. These developments will need to be supported by RSV reference laboratories which can conduct external quality assurance of participating laboratories. It will be essential to ensure that this development does not degrade the quality, completeness or timeliness of data on influenza since the GISRS data represents a vital public health activity eg, in informing annual influenza vaccine composition and in pandemic preparedness. Thus, it would be prudent to start with pilot projects in a few countries in each global region supported by a few designated RSV reference laboratories and this is the approach currently being proposed by WHO [6].

In high-income countries, in addition to the approach noted above, other options could be feasible. These could include bespoke hospital-based surveillance schemes focused on RSV or, as in Canada (in their Serious Outcomes Surveillance (SOS) and Immunization Monitoring Program ACTive (IMPACT) paediatric surveillance network [7]), be part of a broader hospital surveillance scheme targeting a number of infectious diseases such as rotavirus, pertussis and RSV. Setting up such a new surveillance system would be an expensive and technically demanding challenge which will have to be developed in a step wise manner focussing on training, capacity building and provision of technical resources. In Europe, the European Centre for Disease Control (ECDC) held a meeting of an RSV Task Force in 2003 and more recently a consultation on RSV surveillance in November 2015. The 2003 Task Force concluded that RSV surveillance was feasible in Europe based on the experience of reporting RSV disease episodes in 6 European countries and recommended that future real-time data on RSV should be possible to provide through the European Influenza Surveillance System (EISS) reporting infrastructure [8]. The 2015 consultation reviewed the current status of RSV surveillance in Europe and started discussion with a wide range of national public health agencies on how this could develop in Europe in the next few years. These developments in surveillance will need to be accompanied by investment in new cohort studies to better understand RSV epidemiology and burden of disease.

Reductions in mortality from childhood pneumonia have been the largest single contributor to global falls in postneonatal child mortality over the past decade and have been due to a variety of factors associated with socio–economic development as well the introduction of new vaccine and other interventions. The development of effective new vaccines and other prevention strategies to tackle RSV have the potential to make major contributions to reducing severe disease and deaths from RSV in children globally. These developments may also have an important impact on cardio–respiratory sequelae due to RSV associated with from the growing tide of non communicable diseases among middle aged and elderly adults globally. It is important that structured data gathering systems are put in place now to gather the essential data that will be required to provide a secure evidence base to guide national, regional and global policy decisions in the near future.

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Africa

>> The European Medicines Agency has cleared the world's first malaria vaccine, prior to prior to its approval for use in Africa. The vaccine (Mosquirix) was developed by Glaxo-SmithKline, who have pledged not to profit from the vaccine. It is designed to target infection in children in Africa, although it does not appear to be very effective in protecting young babies - children aged 5-17 months seem to benefit the most, with a 33% reduction in cases over four years. Unfortunately, the vaccine cannot be administered alongside other childhood vaccines, and children must receive all shots (including a booster shot) to benefit. However, even a partially effective vaccine can help countries with high infection rates. Prof Adrian Hill of the Jenner Institute, Oxford said "a bed net is more effective that this vaccine, but nonetheless it is a very significant scientific achievement. I see it as a building block towards much more effective malaria vaccines in years to come." (BBC, 24 Jul 2015)

➤ The Islamic Development Bank (IBD) has pledged US\$ 360 million of financing to support the post-Ebola recovery effort in Sierra Leone and Guinea. The announcement was made at the UN-organised International Ebola Recovery Conference, held in New York in July 2015. Guinea would receive US\$ 220 million and Sierra Leone US\$140 million. Liberia is not a member country of the IBD, but the IDB will support post-Ebola recovery by strengthening partnership through other agencies such as the Arab Cooperation Group. The late King Abdullah of Saudi Arabia had also donated US\$ 35million to the IBD to support the countries affected by Ebola. (*allafrica.com*, 28 Jul 2015)

► The global disease burden for conditions treatable by surgery is twice that of HIV/AIDS, malaria and TB combined – and 1–in–3 of the world's population has no access to surgery. Surgery is also dangerous without appropriate equipment and training–including basic equipment like pulse oximeters, which risks 6 million lives each year. Uganda is working to rectify this by introducing several innovations and improvements. First, surgeons are using simple, cheap and innovative drill covers to perform orthopaedic surgery using household drills. The NGO Lifebox has distributed cheap and simple pulse oximeters across Ugandan hospitals. Ugandan hospitals are also adopting the WHO's surgical safety checklist, which can cut death rates and surgical complications by more than 30% by reducing the most common errors. (*Al Jazeera*, 17 Aug 2015)

>> South–east Sierra Leone has been free of Ebola for six months, whereas it continues to linger in the north-west of the country. This is puzzling, as the north-west has received more foreign aid. The south-east is more isolated, which may explain part of its success, but other factors could be more important. In the south-east, prominent locals, doctors, priests, political leaders and chiefs played larger roles in fighting Ebola. In the north-west, Ebola efforts were managed by a politically-appointed co-ordinator, who side-lined non-medical people and traditional healers. By summer 2015 this had improved, with agencies working more closely with traditional and political rulers. Chief Vangahun, one of the south-east's paramount chiefs at the forefront of the region's battle against Ebola, commented that "pouring money into the fight against Ebola does not solve the issue." (The Economist, 29 Aug 2015)

>> The WHO's global status report on road safety shows that 1.25 million people die each year from road traffic accidents. The risks of dying largely depends on where people live and how they move around. Africa has the highest death rate from road accidents, although all low-and middle-income countries are disproportionately affected by road deaths, despite having fewer vehicles per capita. Countries with the most success in reducing this toll have introduced better legislation, stricter enforcement, and safer roads and vehicles. Although road deaths are stabilising, more must be done to tackle these generally-preventable deaths, including improved public transport and preventing pedestrian deaths and injuries by making cycling and walking safer. "Road traffic fatalities take an unacceptable toll-particularly on poor people in poor countries," says Dr Margaret Chan, the WHO Director-General. (Ghana Business News, 19 Oct 2015)

Asia

According to the Internal Displacement Monitoring Centre's (IDMC) annual report, 19 million people were displaced by natural disasters in 2014 (eg, floods and earthquakes), a decrease from 32 million in 2012. More than 90% of these displacements were in developing countries, with China, India and the Philippines experiencing the most displacement. This disguises a rising trend, as the average number of people displaced each year for every million inhabitants has doubled since 1970. The IDMC statistics may under–report smaller incidents, and slower–onset incidents (eg, environmental degradation and drought) are not included. The IDMC states that improved monitoring and data are essential to measure the effectiveness of disaster management initiatives and development, especially due to the growing risks posed by urbanisation and climate change. However, the rise in displacement may mask a more positive trend – fewer people are dying in natural disasters, with the Philippines in particular improving in pre– emptive evacuation. (*scidev.net*, 30 Jul 2015)

Following a meeting with government officials, opposition party leaders and ethnic minority groups, Myanmar announced an ambitious target to eliminate malaria in the country by 2030 - at an estimated cost of US\$ 1.2 billion. The range of stakeholders reflects a rare consensus over a major challenge. Malaria is a huge burden on Myanmar's people and economy. Myanmar is a bridge between southeast Asia-where strains resistant to artemisinin first took hold-and India, from which it could spread to Africa and beyond. Malaria cases have fallen from 300000 in 2013 to 250 000 in 2014, as Myanmar moves from control to eradication. Ahead of the country's elections in Nov 2015, the leader of the National League of Democracy, the main opposition party affirmed his support. "Whoever wins the coming election, this malaria elimination program will go on, because there will still be this disease threatening our country," said Dr Tin Myo Win. (The Irrawaddy, 5 Aug 2015)

▶ According to UNICEF's *Promise Renewed: 2015 Progress Report*, Indonesia has made substantial progress in reducing child mortality. In 1990, there were 85 deaths per 1000 births for children aged under 5 years, falling to 27 per 1000 births by 2015. This represents 5 million lives saved over the period. This success is due to expanding immunisation, promoting breast–feeding, the prompt diagnosis and treatment of common childhood illnesses–all underpinned by strong economic growth. "Saving the lives of

millions of children is one of Indonesia's great achievements over the past 25 years," said UNICEF representative Gunilla Olsson. She noted that further reductions will depend on addressing other issues, such as premature birth, severe infections and asphyxia. (*TEMPO*, 9 Sept 2015)

Médecins sans Frontières (MSF) is calling for an independent humanitarian commission to investigate the bombing of an MSF hospital in Kunduz, Afghanistan, regarding it as a war crime. The bombing killed 22 people, and left thousands of people without health care. The US military took responsibility for the air strike, admitting that it was a mistake. President Obama apologised directly to the MSF president Dr Joanne Liu, and offered his condolences. This would be the first time that such a commission (created under the Geneva Convention in 1991) will have been activated. The USA has launched a separate investigation into the bombings. However, "if we let this go, as if it was a non-event, we are basically giving a blank cheque to any countries who are at war. If we don't safeguard that medical space for us to do our activities, then it is impossible to work in other contexts like Syria, South Sudan, like Yemen," says Dr Liu. (*Reuters*, 7 Oct 2015)

>> North Korea received US\$ 21.3 million in humanitarian aid in the first six months of 2015 (US\$ 9.64 million of food aid, US\$ 6.2 million of health care, and US\$ 2.4 million of drinking water). However, there are severe shortages of medicine in the country, with more than 80% of village clinics suffering from chronic shortages of supplies, despite the state's guarantee of free universal health care. This has led to counterfeit versions of donated medicines flooding local markets. These fake medicines, labelled as "UN medicines" to disguise their origins, are dangerous to patients, and undermine trust in genuine donated supplies. Much donated aid has also been seized by the country's elite, leading to debate about the wisdom of sending aid. However, others argue that some supplies will eventually reach the wider population, thus providing some benefit. (Radio Free Asia, 2 Nov 2015)

Australia and Western Pacific

Experts warn that Australia is experiencing an epidemic of hepatitis C, with nearly 250 000 people infected by the blood–borne virus. 90% of new infections are amongst injecting drug–users, despite increased efforts to ensure access to clean syringes. Hepatitis C can remain undetected for years, but if left untreated it will attack the liver and can lead to cirrhosis, liver disease and liver cancer. Although treatment options are improving, they are expensive and many are afraid of the side effects. An estimated 10000 people contract the virus each year, and 700 people die from the associated liver diseases. Drugs support groups call for improved access to clean injecting equipment, such as more access points, after–hours access, increased education and removing legal barriers to the peer distribution of injecting equipment. (*ABC*, 28 Jul 2015)

>> The Trans–Pacific free trade agreement currently being negotiated by 12 Pacific Rim countries (Australia, Brunei, Canada, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, the US and Vietnam) could threaten the affordability of generic medicines, and undermine the HIV response in developing countries. The Foundation for AIDS Research (amfAR) warned that the TPP could delay generic drugs becoming available on the market by expanding intellectual property protection for existing pharmaceutical drugs, hence keeping prices high. Generic medicines have been crucial in expanding the antiretroviral treatment for HIV-positive people in developing countries. "If the TPP moves forward, it will set a dangerous global precedent and put life-saving drugs beyond the reach of millions of people with HIV/AIDS, cancer, tuberculosis and hepatitis C," said Kevin Robert Frost of amfAR. (The People's World, 25 Aug 2015)

Australia is the only developed country not to have eliminated trachoma, an infectious eye disease. Trachoma is endemic amongst Australia's remote Indigenous communities. It causes inverted eye–lashes which painfully scratch the cornea and could eventually cause blindness. Nick Martin, the Director of Public Affairs at the Fred Hollows Foundation, believes that trachoma is part of a bigger issue for Indigenuous people, and that gaps in housing and access to services for Indigenous people must be closed. Globally, the WHO is aiming to eliminate trachoma by 2020. "It remains a disgrace that trachoma is still endemic in Indigenous communities in Australia; it should not be happening in the 21st century and that is why we have to press onto 2020 for elimination," says Nick Martin. (*The Diplomat*, 3 Sept 2015) ▶ Australia's highest court has ruled that BRCA–1, a breast–cancer gene, cannot be patented. This follows an appeal by Yvonne D'Arcy, an Australian breast cancer survivor, against a US–biotechnology company, Myriad Genetics. Ms D'Arcy argued that allowing corporations to own human gene patents stifled cancer research, the development of treatments for genetic diseases, and that Myriad could charge high prices for testing for the BRCA1 mutation. Myriad's counter–argument is that patents ensure innovation could be commercialised for everyone's benefit. Prior to this case, the US Supreme Court had ruled that genes are not patentable. (*Xinhua*, 7 Oct 2015)

>> At a summit in Fiji ahead of UN climate talks in December. the Pacific Island nations called for the world to address the health impacts of climate change on these islands. The Fijian health minister, Rata Inoke Kubuabola, said that Fiji was dealing with re-emerging climate-influenced diseases eg, typhoid, dengue fever, leptospirosis etc. In 2014, dengue fever infected 20000 people in Fiji. Almost all Pacific Island nations are expected to attend the meeting, where they will call for the world to act decisively to address climate change. They are critical of industrialised nations who they perceive to risk the entire planet to protect their economies and standard of living, at the expense of the Pacific Islands and other parts of the world-who are not responsible for climate change. "We say if you save Tuvalu you save the world, because if you bring down emissions enough to save us, the rest of the world will be OK," says Santini Tulaga Manuella, Tuvalu's health minister. (The Guardian, 2 Nov 2015)

China

>> Universal health coverage is unusual in developing countries, but China went against this trend by implementing universal health insurance coverage (UHIC) in 2011. In a paper published in *Health Policy*, Hao Yu argues that this coverage, the largest–ever expansion of UHIC, was driven by several factors. First, the SARS outbreak in 2003 highlighted the country's under–investment in health. There is strong public support for government intervention in health care, coupled with increased political support for addressing health care. UHIC is heavily subsidised, with the government covering 75–85% of costs; and China's strongly–performing economy enables this investment in UHIC. Local governments were given targets and incentives to extend coverage and enrolment, including their own performance evaluation. Lastly, China used a successful two–pronged approach to implementing UHIC, first achieving wide but shallow coverage, then expanding benefits. China now faces the challenges common to UHIC systems–quality improvement and cost control. (*Health Pol-icy*, 28 Jul 2015)

▶ China's government has launched a new three-year programme to cut the number of under-age drug users, and to raise awareness amongst young people. The average age of drug users in China has fallen, and 1.89 million registered drug users are younger than 35 years-58% of the total number of registered users. The programme will target young people aged 10-25 years, and its large-scale awareness campaign will reach all students. It aims to keep the number of underage drug offenders at less than 0.3% of all drug offenders, and achieve a "notable reduction" in new users. Liu Yuijin, the deputy director of China's National Narcotics Control Commission, pledged that the government will treat the programme as a priority over the next three years. (*Xinhau*, 30 Jul 2015)

According to a report published by the consultancy firm Clearstate, the health care market in China is undergoing structural change driven by health care reforms, market dynamics and the changing needs of patients in China. Clearstate predicts five key trends that will affect the health care sector by 2020. First, new service providers will emerge, driven by private insurance creating demand for services beyond public hospitals. Second, China's private insurance market is set to grow by 25–30% for the next 5 years, fuelled by an increasing number of wealthier individuals and enterprises. Third, the government classifies the medical device industry as a priority industry, and plans to support strong domestic pharmaceutical companies. Fourthly, there will be increased emphasis on prevention (eg, screening programmes for chronic diseases) and health management. Lastly, China is set to become the world's second-largest mobile-health market, growing by 60% from 2015 to 2018. This is driven by people's need for reliable health information beyond the limited amount doctors can provide physicians being unable to provide time beyond diagnosis and treatment, and the use of mobile health in

Europe

European governments are working together to negotiate prices for pharmaceuticals, in the hope that the higher volumes will lead to lower prices. Current partnerships are responding to particular domestic circumstances, but the formation of these bargaining blocs has led to renewed calls for an EU-wide way of negotiating with pharmaceutical companies to help reduce high drug prices. Industry bodies believe that such negotiations should be national, although they admit there is scope for some flexibility. There are advantages in an EU-wide pricing system, but the chances of reaching agreeing on one are remote because health care is seen as a national issue, and the difference between EU economies is too great. From a pharmaceutical perspective, a single European decision-making process would increase the risks of drug development. However, the trend towards joint negotiation could spread, although pharmaceutical companies will try to separate them. (Economist Intelligence Unit, 4 Jun 2015)

▶ Greece's financial crisis has had a massive impact on its health care system. State hospitals have cut budgets by up to 50%, basic items such as gloves and syringes are in short

rural areas to overcome accessibility difficulties. (*Economist Intelligence Unit*, 5 Oct 2015)

>> Taiwan's Centers for Disease Control reported suspected 19 deaths from dengue fever. Of the 19 suspected deaths, 18 were from Tainan and one from Kaohsiung. 18 of the 19 people also suffered from chronic diseases. Dengue fever has been especially prevalent in Tainan in 2015, with 3234 confirmed cases this year, accounting for most of the 3686 cases reported throughout Taiwan since 1 May 2015. The government is spreading pesticides and pumping seawater into drainage systems to control the mosquito population which spreads the disease. (*China Post*, 2 Sept 2015)

▶ Parts of China was covered in smog as levels of the most dangerous particulate PM2.5 reached the highest recorded levels for 2015, and were almost 50 times higher than the WHO's recommended limits. 21 cities experienced high levels, with the Shenyang city government issuing a "level 1 high alert" emergency response, which includes schools banning outdoor activities, asking residents to use "green transport", and to stay indoors and take health precautions. China's air pollution is linked to hundreds of thousands of early deaths, and can cause heart disease, stroke and lung diseases. The smog was caused by a surge in coal-powered heating ahead of winter, and heavy pollution being blown in from other provinces. (*South China Morning Post*, 9 Nov 2015)

supply, and the number of doctors and nurses is critically low. Rising unemployment and poverty has left 2.5 million Greek people without health coverage, and screening programmes have been slashed, leading to more diseases being diagnosed at a later stage. Pharmacist are dealing with delays in government payments, difficulties in sourcing imported drugs due to disruptions in the supply chain, and a shortage of funds. Many Greek nationals are relying on voluntary health care staff – previously the preserve of refugees or other nationals with no health care access. "We're already facing a humanitarian crisis in Greece. Of all the damage done during the last five years, health care has been hit the worst," says Dr Sofia Garane, a clinic manager from the NGO Doctors of the World. (*The Guardian*, 9 Jul 2015)

▶ Research on e-cigarettes, commissioned by Public Health England and led by Prof Ann McNeill of King's College London and Prof Peter Hajek of Queen Mary University of London, has found that they are 95% less dangerous than traditional cigarettes. E-cigarettes may also contribute to declining rates of smoking, and could be an effective intervention to reduce smoking in groups where it is highest. "While smoking cessation services continue to be the most successful way to help people stop smoking, the highest successful quit rates are being seen among smokers who are also using e–cigarettes. Providing health care professionals with accurate advice and information on their use is necessary if we are to unlock the full potential of e–cigarettes in helping people to kick their habit," says Prof Penny Woods of the British Lung Foundation. (*Medical News Today*, 19 Aug 2015)

Human rights campaigners warn that Armenia's mental health laws are open to abuse, contain incentives to detain people unnecessarily, and make it too easy to declare people mentally incompetent. The laws are a relic from Armenia's Soviet period, where detention in mental institutions could be used to silence trouble-makers. One phone call to the police or a psychiatric unit is sufficient to have someone hospitalised; and if the person refuses to be admitted the courts can be applied to for mandatory admission, without the patient being represented. There is no requirement to periodically review initial assessments, and high payments for hospitalisations create incentives for hospitals to admit and keep patients. Tatevik Khachatrian, Armenia's state deputy ombudsman, calls for complete revision of the laws, saying that "we have registered cases when people with no mental illness were locked away in institutions

India

▶ India has more malnourished people than any other country, and 30% of its children are underweight-albeit an improvement on 43% in 2002 - compared to 3% in China. Malnutrition weakens people and renders them more vulnerable to disease, and stunts brain development in children. The Indian government is making limited progress in fighting hunger, due to taboos, corruption and political pride. Measures such as free school lunches have helped, but there are problems of rotten food, stolen subsidies, and banning certain foodstuffs (eg, high-protein eggs) due to dietary restrictions. The Indian government has not published the results of a joint UN survey on child nutrition, hindering states' ability to learn from each other. Critics suspect its suppression may be due to its criticism of Gujarat, the home state of Narendra Modi, India's Prime Minister. The government should publish all data that could lead to better policies to tackle malnutrition, and focus on girls and women, who are more likely to be malnourished than men and boys. (The Economist, 4 Jul 2015)

According to the WHO, the malaria parasite *P. vivax* is causing a high disease burden in India. In 2013, there was

where they were tied up and abused." Julietta Amarikian was nearly hospitalised when her brother attempted to have her detained in a psychiatric unit following a family dispute. With the help of a human rights activist, she successfully appealed, but her case highlights the dangers of government inaction on Armenia's arcane mental health laws. (*The Guardian*, 12 Oct 2015)

According to the OECD's annual Health at a Glance 2015 report, the UK has one of the worst health care systems in the developed world. Too many lives are being lost because the quality of care is not improving quickly enough. Cancer survival rates are improving, but still remain in the lower third of OECD countries for some cancer types, and acute care is average. The UK had insufficient staff to ensure basic procedures are being followed, with a poor record on hospital-acquired infections. The UK also lags behind in life expectancy at birth, and in containing obesity in adults and children. This is partly due to the UK spending less on health care than other OECD countries, and too much attention on institutional structures and too little on making the basic processes of care work better. A Department of Health spokesperson claims to be prioritising investment in frontline NHS services, with an additional 10500 doctors and 7600 nurses since May 2010, and aims to make the NHS the world's safest health care system. (International Business Times, 5 Nov 2015)

an estimated 15.8 million symptomatic cases of P. vivax worldwide, with 67% occurring in south-east Asia, which includes India, where over 50% of cases are caused by this parasite. However, there is a small fall in malaria cases caused by the more dangerous P. falciparum parasite. To date, anti-malaria efforts have focused on the P. falciparum strain, but it now recognised that this must be broadened to P. vivax, which the WHO estimates could be responsible for up to 15% of malaria deaths outside Africa. P. vivax is unresponsive to existing control measures, and can remain hidden and beyond the reach of current diagnostic tools and medication. "We need targeted strategies for P. vivax malaria which presents distinct challenges for control and elimination compared to P. falciparum," says the WHO Regional Director, Poonam Khetrapal Singh. (The Times of India, 30 Jul 2015)

>> There are concerns that India's proposed changes to its intellectual property legislation could threaten the provision of cheap, life–saving drugs to sub–Saharan Africa. India protects drug–making processes not products, allowing pharmacists to "reverse engineer" drugs with different pro-

cesses and offer cheaper, generic copies. However, India is being pressurised by the USA to protect data produced when developing a drug. This would outlaw compulsory licensing of (and may even restrict) generic versions of offpatent drugs. An estimated 80% of antiretroviral drugs in Africa are from India, which supplies 17.7% of Africa's pharmaceutical imports. This helped India's pharmaceutical industry to grow to US\$ 19.36 million each year. It is argued that India should resist US pressure by reminding it that its generics are mainly sold in developing countries, so it is not a threat to the US's core markets. There could also be profitable partnership opportunities, if Indian firms would offer their expertise about trading in Africa (whose pharmaceutical market will be worth an estimated US\$ 30 billion by 2016) in exchange for R&D resources. (scidev. net, 28 Aug 2015)

▶ In January 2015, the Indian government consulted on tighter laws on tobacco control, eg, raising the minimum smoking age to 21 years, and banning the sale of single cigarettes, which account for 70% of sales. Each year, 1 million Indian people die from smoking-related causes-making it one of the most common causes of death. India spends US\$ 15.9 billion on treating smoking-related illness each yearalmost six times the amount raised through tobacco tax revenues. Taxes on Indian cigarettes have increased sharply to 60% of the retail price–approaching the WHO recommendation of 75%. However, India's traditional bidi cigarettes have largely escaped these curbs. Bidis are taxed at 7% of their retail price, although bidi cigarettes are riskier than conventional cigarettes as they are inhaled more deeply. According to the Public Health Foundation of India, doubling taxes on bidis could cut consumption by 40%, and increase tax revenue by 22%. In addition, people making bidi cigarettes are generally under–paid, and face a range of health problems (including cancer), as masks and gloves are not used. (*Indiaspend.org*, 1 Sept 2015)

▶ In an interview with India's *Economic Times*, Bill Gates spoke of how India can make progress in reaching the new Sustainable Development Goals (SDG). He praised India's progress in achieving some of the MDG targets, and outlines the importance of quality primary health care for India, which must be robust and fully functional. He believes that this will help close the gap on preventable deaths in India, which disproportionately affects the poorest people. Overall, he highlighted the MDGs' tangible results, such as the sharp falls in child and maternal mortality. He is optimistic that the SDGs will build on this to eradicate extreme poverty and hunger, foster inclusive economic growth and combat climate change by 2030. (*Economic Times of India*, 30 Sept 2015)

The Americas Cuba has become the first country to receive WHO validation for eliminating (ie, a reduction in transmission to a level that does not threaten public health) mother to child

idation for eliminating (ie, a reduction in transmission to a level that does not threaten public health) mother-to-child transmission of HIV and syphilis. PAHO has worked with Cuba and other countries to roll out a programme to eliminate this transmissions. Measures include improved access to prenatal care, more screening for pregnant women and their partners, caesarean deliveries and substituting breastfeeding. Globally, 1.4 million HIV-positive women become pregnant each year, and antiretroviral treatment reduces the risk of transmission from 15-45% to 1%. In welcoming the validation, Michel Sidibé, the UNAIDS executive director said that "this is a celebration for Cuba and a celebration for children and families everywhere. It shows that ending the AIDS epidemic is possible and we expect Cuba to be the first of many countries coming forward to seek validation that they have ended their epidemics among children." (IPS, 30 June 2015)

▶ From 2002 to 2013, US deaths from heroin overdoses rose from 0.7 to 2.7 per 100000 of population. Rates of use, abuse and dependency increased to 517 000 by 2013–

a 150% increase from 2007. Rates are highest amongst males, those aged 18-25 years, people living in urban areas, poorer people and people without health coverage. However, rates increased across all groups over the period. Most overdose deaths involved multiple drugs, and the relationship between heroin and cocaine use is particularly strong. The increased availability, lower price and higher purity of heroin is a potential contributor to the rise, and it is vital that public health works with law enforcement to counter the crisis. Any responses must focus on reducing the rates of non-medical use opioid pain relievers, as the rates of initiating heroin use in this group are 19 times higher than those outside it. It is also vital to improve health insurance coverage to heroin users, in order to reduce usage and addiction, and to reduce HIV and hepatitis transmission. (CDC, 7 Jul 2015)

▶ Bioven, a Malaysian biotech company, will seek an Initial Public Offering (IPO) to raise funds for marketing a promising cancer drug which was developed in Cuba. The IPO is expected to raise US\$ 30–35 million for the drug, which targets non–small cell lung cancer. Phase III trials involving 419 patients across 10 countries are under way, and a separate trial will take place in the USA under the guidance of the Roswell Park Cancer Institute. More clinical development is under way at the Beatson Institute for Cancer Research in Glasgow, UK. (*Xinhua*, 30 Jul 2015)

Former President of the USA, Jimmy Carter, recently announced that his cancer had spread to his brain. He also spoke about his non–profit Carter Center's work to combat guinea worm disease. The Carter Center began this work in 1986, when there was 3.5 million cases across 21 countries. Infection from the water–borne guinea worm is painful, and can take months of recovery. Thanks to educational campaigning on the importance of filtering water and avoiding submerging guinea worm lesions in water, there are now only 11 cases left worldwide. When it is wiped out, guinea worm disease will join smallpox as the second

human disease to be eradicated. "I'd like the last guinea worm to die before I do," said Mr Carter. (*Huffington Post*, 21 Aug 2015)

▶ According to PAHO, malaria cases and deaths have fallen sharply across Latin America, with Brazil, Honduras and Paraguay showing the most progress. Cases have fallen by nearly 70%, from 1.2 million in 2000 to 375000 in 2014, and malaria deaths fell by nearly 80% over the same period. PAHO praised Brazil's national prevention programme. Worldwide, control and prevention techniques have led to a 60% reduction in mortality rates since 2000. However, 438000 people died from malaria in 2014–and 91% were in sub–Saharan Africa. The UN aims to cut the numbers of malaria cases and deaths by a further 90% by 2030, which will require an increase of funding from US\$ 2.7 billion to US\$ 8.7 billion. (*Thomson Reuters Foundation*, 6 Nov 2015)

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• The Bill and Melinda Gates Foundation

Each year, 6.3 million children die before their 5th birthday - a 50% reduction compared to 1990. The BMGF aims to reduce this by a further 50%, with a US\$ 776 million investment in child nutrition. According to the BMGF, under-nutrition is a major factor in half of child deaths, and it will invest in prevention strategies. These will include providing seeds and technical expertise to harvest fortified crops, agricultural techniques which conserve soil and water, training in agricultural techniques and expanding internet access to share information on crop prices and market conditions. Extra efforts will be made to reach women farmers - 50% of African farmers - who are 90% more likely to re-invest additional income in the family compared to men. The BMGF will also support the education of young women and adolescent girls about proper diet and the importance of breastfeeding, in recognition that the first 1000 days from conception are crucial for long-term physical and mental development. The BMGF will focus on India, Ethiopia, Nigeria, Bangladesh and Burkina Faso, and there will be partial matched funding from the UK. The EU has pledged US\$ 3.8 billion by 2020 to fight child malnutrition. (Time, 3 June 2015)

▶ Bill Gates announced plans to invest US\$ 2 billion into breakthrough energy projects that will reduce greenhouse gas emissions and bypass fossil fuels. Mr Gates has already invested US\$ 1 billion in early-stage energy companies that are geared to preventing climate change. In making this investment, Mr Gates argues that existing clean energy sources can only curb global warming at "astronomical" costs, so innovation is desperately needed. It will probably target early-stage clean energy projects, eg, high-altitude wind power, solar chemical power and depleted uranium as a power source. Investment in renewable energy is expected to reach US\$ 8 trillion over the next 25 years, outpacing investment in fossil fuels and nuclear. "Because there's so much uncertainty and there are so many different paths, it should be like the Manhattan Project and the Apollo Project, in the sense that the government should put in a serious amount of R&D," says Mr Gates. (International Business *Times*, 25 Jun 2015)

▶ The BMGF is a part of a major investment in Editas Medicine, which has raised US\$ 120 million to further de-

velop a new technology to edit genes to treat disease. Editas Medicine, based in Cambridge MA (USA), hopes to use the tool CRISPR–Cas9 to allow scientists to hone in on faulty genes and replace with a healthy gene. Katrine Bosley, the chief executive of Editas said "they all appreciate the vast potential of this science. The heart of the conversation we had with everybody is how you translate this very exciting but young science into treatments, into therapies." (*Business Insider*, 10 Aug 2015)

▶ The BMGF has awarded Novavax a grant of up to US\$ 89 million to support the development of the RSV F Vaccine Phase 3 clinical trials in pregnant women. It will also support regulatory licensing efforts towards pre-qualification by the WHO. Novavax will make the final vaccine affordable and accessible to people in the developing world. "Respiratory syncytial virus (RSV) is the leading cause of pneumonia in infants, and currently there are no affordable approaches to protecting children in the developing world. Maternal immunisation may provide protective antibodies to infants during the first few months of life, and we hope this vaccine will protect infants from this disease to help them live healthy, productive lives," said Dr Keith Klugman, director of the BMGF's Pneumonia Program. (*Street Insider*, 29 Sept 2015)

▶ Four years after its introduction, the MenAfriVac vaccine has led to the number of meningitis A cases approaching zero in the epidemic belt across Africa. This area experiences an epidemic of meningitis A every 10-15 years; in 1996-1996 there were more than 250000 cases, 25000 people died and many more suffered from permanent disabilities. Following this, African governments united to demand the development of an effective, affordable vaccine that could be rolled out across the region. There was a lack of private investment, as this strain of meningitis A affects some of the poorest places on earth. However, a partnership between PATH and the WHO led to the Meningitis Vaccine Project, which aims to develop and produce an effective vaccine. The partnership model has no permanent organisation, but is a coalition that is formed anew for each project, and is tailored to its specific needs. The project received US\$ 70 million of funding from the BMGF. (IRIN news, 17 Nov 2015)

• The GAVI Alliance

▶ New figures from the WHO show that the triple–vaccine coverage rate amongst children for diphtheria, tetanus and pertussis was 81% in the 73 countries supported by GAVI. This is a 1% increase from 2013, and 21% increase from 2000, when GAVI was formed. In 2014, all GAVIsupported countries extended their triple vaccines to the pentavalent vaccine, which includes hepatitis B and Haemophilus influenzae type b. There were also significant gains in the coverage for pneumococcal and rotavirus immunisations. However, there are coverage variations between countries, and the sharp falls in Haiti, Côte d'Ivoire and Zimbabwe are particularly concerning. This highlights the importance of understanding these variations, both between countries and at sub-national/community levels. Moreover, the countries most affected by Ebola have experienced falls in coverage, and GAVI is working to help them rebuild their routine immunisation systems. (allafrica.com, 17 Jul 2015)

▶ A trial in Guinea shows that an experimental Ebola vaccine (rVSV-ZEBOV) seems to give total protection, according to a study published in The Lancet. The trial was based on a ring design - used by the smallpox eradication campaign - whereby each patient's close contacts are vaccinated to halt onwards transmission. The vaccine appears to work well for 3 weeks - excellent for an outbreak situation, but there are questions over longer-term protection. The WHO is now considering whether to approve the vaccine for general use. This could enable the vaccine to be stockpiled for future outbreaks. However, GAVI will work with researchers and industry to develop second-generation vaccines, as rVSV-ZEBOV must be stored at -80°C and protects against a limited number of Ebola strains. The second-generation vaccines will target other strains and the closely-related Marburg virus, and do not require expensive storage. "This is illustrating that it is feasible to develop vaccines much faster than we've been doing," says Adrian Hill, a vaccine scientist involved in testing other Ebola vaccines. (Nature, 31 Jul 2015)

▶ Dr Ngozi Okonjo–Iweala, Nigeria's former Minister of Finance was appointed the new Chair Elect of GAVI. Dr Okonjo–Iweala led negotiations with the Paris Club of Creditors in 2005 that led to the clearing of US\$ 30 billion of Nigeria's external debt. She is also a former Managing Director of the World Bank, with special oversight of for Eastern Europe, Central and South Asia, and Africa. Her accolades include *Time* magazine's European Hero of the Year (2004), and being listed as one of the 100 most powerful women in the world by *Forbes*. "I am excited to be joining GAVI during this crucial time. GAVI has a well–earned reputation as one of the leading players in global health, providing services that underpin human and economic development," she says. (*venturesafrica.com*, 21 Sept 2015)

▶ The Republic of Korea has signed an agreement with GAVI to improve its support for childhood vaccinations in some of the world's poorest countries. The Republic of Korea will provide an additional US\$ 3 million between 2015 and 2017. These funds will be used to finance immunisation programmes in 73 countries, designed to protect children against diarrhoea and pneumonia. Mr Lee Yongsoo, of the Republic's Ministry of Foreign Affairs said "health and children are a priority or Korea's development co–operation policy and GAVI is our partner. We will continue to strengthen our co–operation with GAVI in the years to come." (*Vaccine News*, 7 Oct 2015)

Data from the WHO shows a 79% reduction in measles deaths, from 546 800 in 2000 to 114 900 in 2014, with an estimated 17.1 million lives being saved. The reduction is mainly due to expanded vaccine coverage, and is one of the main contributors to reducing child mortality and progress towards MDG4. However, coverage rates have stagnated at 85% between 2010 and 2014 (despite large increases up to 2010) so the 2015 global milestones and WHO measles elimination goal will not be achieved on time. In 2014, mass vaccination campaigns led by governments with support from the Measles and Rubella Initiative and GAVI, reached 221 million children, and since 2000 these campaigns have enabled 2 billion children to receive a supplementary dose of measles vaccine. "Despite the welcome reduction in measles deaths, this highly infectious disease continues to take a terrible toll on the lives of children around the world. A co-ordinated approach that puts stronger routine immunisation at its core will be central to getting measles under control and securing further reductions in mortality from this vaccine-preventable disease," says Dr Seth Berkley, CEO of GAVI. (Business Standard, 13 Nov 2015)

• The World Bank

NEWS

According to Subhash Chandra Garg, the World Bank Executive Director for India, Bangladesh, Bhutan and Sri Lanka, India could become a multi-trillion dollar economy with a per-capita income of US\$ 40000 (compared to its current US\$ 2000) by 2050. This will require economic growth of at least 7% a year over the next 30-35 years, the transformation of India's agricultural sectors, and boosting its tourism, manufacturing, services and health care. People must move out of agriculture into services and manufacturing, whilst ensuring that agricultural production increases. India must exploit its demographic dividend of a large young population, and invest in training these workers to provide exportable skills. Mr Garg noted how the World Bank is partnering with the Indian government through initiatives such as Smart Cities and the Swachh Bharat campaign to realise the vision of a strong and prosperous nation. (Economic Times, 20 Jul 2015)

>> The World Bank approved a US\$ 700 million investment in an offshore gas project in Ghana to address its electricity shortages, which frequently cause power blackouts. This consists of a US\$ 500 million guarantee to support regular gas purchases, and US\$ 200 million to help secure private financing. Gas production is due to start in 2018, with a capacity of 1000MW, and enables Ghana to switch its energy mix from oil to natural gas. This will reduce its yearly oil imports by up to 12 million barrels, and cut yearly CO₂ emissions by 1.6 million tonnes. The IMF had described Ghana's electricity crisis as "the single most important risk" to its economic development. In welcoming the investment, Ghana's finance minister Seth Terkper said "this project is an essential element of the driver towards consolidating our middle-income status, and will help secure our natural gas resources for a more affordable and reliable power supply." (Business Green, 30 Jul 2015)

>> The World Bank Report *Going universal: how 24 developing countries are implementing universal health coverage reforms from the bottom up* shows how universal health coverage (UHC) programmes are reducing the number of people impoverished by health care costs. These programmes, from countries such as Ethiopia, Ghana, Peru, Jamaica and Vietnam, cover more than 2 billion people, and were found to be "new, massive and transformational", although greater investment is required. Both the WHO and World Bank recommend that countries implementing UHC should provide 80% of the population with essential health services, and that everyone should be shielded from impoverishing health payments. Tim Evans, senior director of health, nutrition and population at the World Bank Group, said UHC was a triple win. "It improves people's health, reduces poverty and fuels economic growth," he said. (*Public Finance International*, 25 Sept 2015)

A new report from the World Bank shows that the number of people worldwide living in extreme poverty will fall to 9.6%-or 702 million people-of the world's population in 2015 - the first time it has ever fallen below 10%. In 1999, 29% of all people lived in extreme poverty, falling to 13% by 2012. According to Mr Kim, the World Bank president, the fall is due to strong economic growth in developing countries, coupled with investments in health, education and social safety nets. Extreme poverty was previously defined as living on US\$ 1.25/d, but the World Bank has revised this to US\$ 1.90/d to take account of inflation. This reduction increases the momentum towards ending extreme poverty. However, the World Bank is cautious over the obstacles faced, including the growing concentration of poverty in sub-Saharan Africa and reducing extreme poverty when economic growth falters in emerging economies, although it welcomes the sharp falls in Asia and South America. The development agency, Oxfam, highlighted that 702 million people living in extreme poverty is unacceptably high, and that much needs to be done. (ABC news, 5 Oct 2015)

>> In its report Shock Waves: Managing the Impact of Climate Change on Poverty, the World Bank highlights how climate change could force more than 100 million people beneath the poverty line by 2030, threatening the goal of eliminating extreme poverty. The world's poorest people are more exposed to climate-related disasters (eg, heat waves, flooding and drought), and can lose resources when dealing with these disasters. It is estimated that climate change could increase Africa's food prices by up to 12% by 2030, and 70% in 2080 - devastating for poor households where food is 60% of total expenditure. It calls for money saved on eliminating fossil fuels to be invested in assistance programmes, and warns that without immediate adoption of adaptation, mitigation and emission-reduction policies, rising temperatures and greenhouse gases will devastate vulnerable populations. (Tech Times, 27 Nov 2015)

• United Nations (UN)

According to the UN Millennium Development Goals (MDG) report, the MDGs have lifted 1 billion people out of poverty since 2015, making it one of the most successful anti-poverty movements in history. Sub–Saharan Africa is lagging behind, with most citizens facing several inequality although there has been marked improvements in some areas eg, child mortality. The report urges the continent to accelerate progress, supported by improved tax and revenue collection to fund projects. Overall, the numbers living in extreme poverty fell from 1.9 billion in 1990 to 836 million in 2015. Gender parity has been achieved in many areas, especially in schooling and new HIV infections fell 40% from 3.5 million to 2.1 million. The MDGs will be replaced by new Sustainable Development Goals later in 2015. (*Voice of America*, 9 Jul 2015)

>> According to the UN Electoral Observation Mission, Burundi's infrastructure is not conducive for holding creditable elections. Despite two postponements, the incumbent President Pierre Nkurunziza won a third term. In a statement, MENUB said that the country's Constitutional Court ruling on the President's availability to stand for a third term did not resolve presidential term limits, but instead worsened tensions. There was no balanced media coverage for all political parties, and freedom of expression, debate and assembly were curtailed. Following the elections, 100 people have died in protests and 170000 people have fled the country. (*Sahara Reporters*, 28 Jul 2015)

>> The UNHCR stated that nearly 300 000 refugees and migrants have crossed the Mediterranean Sea to Europe in 2015. People are arriving in groups of 300–400, and up to 3000 asylum–seekers arrive at the Macedonian border each day. Most people are fleeing violence in Syria, Afghanistan and Iraq. People are often exhausted and traumatised on arrival, and need humanitarian assistance. Most refugees head for Germany and Sweden, which accepted 43% of asylum–seekers. Germany expects to receive 800000 refugees in 2015. A UNHCR spokesperson, Melissa Fleming, says that this is not sustainable and that a more decent and humanitarian distribution of these people amongst Europe's 28 member nations is needed. The UNHCR also calls for improved legal avenues, eg, more student and work visas, and resettlement opportunities, to lessen the number of people undertaking these dangerous journeys. (*Voice of America*, 25 Aug 2015)

▶ According to the UN, the Taliban's insurgency is at its widest since 2001, earlier rating the threat level in half of Afghanistan's districts as either "high" or "extreme". The Taliban has inflicted ambushes and roadblocks on Highway One, a ring–road connecting Afghanistan's major cities, and have repeatedly cut the highway in government strong-holds. In many areas that are technically under government control, government forces hold only the government buildings and are under attack from insurgents. The UN data suggests increased Taliban activity in areas with hitherto limited presence. The UN has evacuated some staff from Afghanistan, and other aid agencies are following this. (*New York Times*, 11 Oct 2015)

▶ Ban Ki-Moon, the UN Secretary-General, congratulated Aung Suu Kyi over the National League for Democracy's (NLD) victory in Myanmar's elections. Mrs Suu Kyi is the NLD chairperson, and the NLD won over 50% of the seats in the Union Parliament. Ban said that the UN would support Myanmar's democratic reform, and hailed the elections as a "defining moment in the reform process, and have opened up real potential for Myanmar to thrive as an inclusive, harmonious, multi-ethic and multi-religious democracy." (*Xinhua*, Nov 2015)

UN AIDS and The Global Fund

▶ According to UNAIDS, the goal of 15 million people on HIV treatment by the end of 2015 was reached in March–9 months ahead of schedule. This compares to fewer than 700 000 people in 2000. The global response has prevented 30 million new infections and 8 million deaths since 2000. New infections fell from 2.6 million per year to 1.8 million, and AIDS–related deaths fell from 1.6 million to 1.2 million over the same period. Global HIV investment has risen from US\$ 4.8 billion to US\$ 20 billion. Despite this, progress has been slower in some areas, with HIV status awareness being a major barrier to treatment and treatment for HIV–positive children lags behind adults – although the gap is narrowing. Ban Ki–moon, the UN Secretary–General, says "the world has delivered on halting and reversing the AIDS epidemic. Now we must commit to ending the AIDS epidemic as part of the Sustainable Development Goals." UNAIDS recommends front–loading investment to "sprint" towards the target of ending the AIDS epidemic by 2030. (*BBC*, 14 Jul 2015)

>> A statement by the UNAIDS Executive Director, Mr Michel Sidibé, announced a 3.5% reduction in the cost of HIV early diagnostic tests for children, bringing them to US\$ 9.40. This reduction, in partnership with Roche Diagnostics, will help scale-up diagnostic and treatment services for HIV-positive children, in line with the 90-90-90 target [ie, by 2020, 90% of all HIV-positive people will know their status; 90% of all HIV–positive people will receive sustained antiretroviral therapy; and 90% of all people receiving antiretroviral therapy will have viral suppression]. The WHO recommends that all children exposed to HIV receive screening within the first two months of life, but currently screening only reaches 50% of these children due to financial constraints. This had led to a major gap in HIV treatment access, with 32% of HIV-positive children receiving antiretroviral treatment, compared to 41% of adults. Without treatment, 50% of HIV-positive children would die by the age of 2 years, and the majority of the remaining 50% would die by the age of 5 years. (allafrica. *com*, 20 Jul 2015)

>> Dr Adesina Fagbenro, the Southwest Co–ordinator for the UK's Department for International Development (DfID) warned that Nigeria is at risk of losing access to the US\$ 400 billion Global Fund. The warning was prompted by Dr Fagbenro's concern that the government is failing to understand the technical issues around accessing the fund. He stated that it is difficult to access data from ministries and other agencies in many states—and the lack of data evidence will hamper the presentation of a planning proposal. "We have to track the indicators and measure our performance on such issues. Lagos is now enjoying the status of being able to receive budget support. It is only when progress is noticed that international financing agencies will come around to support you. If you don't get it right, you cannot get the needed support," said Dr Fagbenro. (*The Nation*, 25 Aug 2015)

▶ At the Oct 2015 G7 summit, health ministers from the G7 group of most developed countries agreed to the Berlin Declaration on Antimicrobial Resistance, which aims to support LMICs to develop national antimicrobial resistance plans. This requires a three–fold approach: improving infection prevention; protecting the effectiveness of existing and future antimicrobials; and researching new antimicrobials, vaccines, treatment alternatives and rapid diagnostic tools. The ministers also committed to learning lessons from Ebola, and reiterated their support for the WHO International Health Regulations. They have offered to work with 60 countries to implement IHR. The G7 ministers will work closely with organisations such as the Global Fund, GAVI and WHO on this initiative. (*Intellectual Property Watch*, 12 Oct 2015)

>> At the opening session of the 19th European AIDS conference, Prof Kazatchkine (the UN Special Envoy on HIV/ AIDS in Eastern Europe and Central Asia) called for Europe to increase HIV prevention and treatment activities to meet the UNAIDS target of 90% of those diagnosed with HIV to receive treatment, and 90% of those on treatment to have fully suppressed viral loads by 2020. This would result in 73% of HIV-positive people having undetectable viral loadif this target is achieved by 2020 it would end the AIDS epidemic by 2030. Eastern Europe, Central Europe and Western Europe have different experiences of the HIV epidemic. In Eastern Europe, HIV is more prevalent amongst people who inject drugs, although heterosexual transmission is increasing - and prevention and harm reduction services are limited. HIV is concentrated amongst gay men and injecting drug users in central Europe, with limited services provided to those groups. And Western Europe has a stable infection rate, despite strong health care and support. Prof Kazatchkine calls for intensified efforts and more resources to tackle HIV, and to understand and address weaknesses in the current response. (aidsmap.com, 22 Oct 2015)

• UNICEF

▶ UNICEF's report 2014 State of Children in Pakistan shows that 7.1% of Pakistan's children die before their 1st birthday, and 9.1% of children die before their 5th birthday. Although these statistics are a massive improvement on 1990–when 10.6% of children died before their 1st birthday, and 13.8% died before their 5th birthday–they are much worse than comparable countries eg, India. The report states that a lack of clean drinking water and sanitation are two of the biggest hurdles in reducing child mortality. Children growing up in poverty are also less likely to access basic services, or to benefit from preventative initiatives or protection mechanisms. (*Express Tribune*, 9 Jul 2015)

>> According to UNICEF, more than 70 000 births in Liberia went unrecorded due to the Ebola crisis—a 40% reduction compared to 2013. The fall in registrations is caused by the closure of maternity wards as health workers were infected with the virus. However, births may also have fallen during the outbreak which could be a contributing factor. UNICEF is working with the Liberian government to register all babies unrecorded during the epidemic, and to help rebuild the country's shattered health system. "Children who have not been registered at birth officially don't exist. Without citizenship, children in Liberia, who have already experienced terrible suffering because of Ebola, risk marginalisation because they may be unable to access basic health and social services, obtain identity documents, and will be in danger of being trafficked or illegally adopted," says Sheldon Yett, UNICEF's representative in Liberia. (*Yahoo news*, 31 Jul 2015)

▶ In an open letter published in the *Huffington Post*, Anthony Lake, Executive Director of UNICEF, addressed a girl born into poverty during September 2015. This is the month when world leaders meet about the Sustainable Development Goals. These goals should give this girl—and the other 500 million children living in extreme poverty – the same right to a fair chance in life, and to close the gap between their prospects and those who are better off. He called on these children to hold world leaders accountable for any failures to meet these goals. He also addressed a boy not born into poverty during September 2015, to remember that these goals are universal goals and to also hold world leaders accountable for any failure. (*Huffington Post*, 1 Sept 2015) ▶ A joint release from UNICEF, the World Food Program and the Food and Agriculture Programme calls for unrestricted humanitarian access to prevent famine in parts of Unity State in South Sudan. The 2-year civil war has left nearly 4 million people at risk of starvation, and aid agencies are struggling to reach these people. Fighting in South Sudan has displaced more than 2 million people, and livelihoods have been devastated by high inflation rates, market disruption, displacement, loss of livestock and agricultural production. Food shortages are exacerbated by pending harvest shortfalls in Uganda, the Sudan and Ethiopia, which will further increase food costs in South Sudan. (*Humanosphere*, 2 Nov 2015)

>> More than 500000 children face life-threatening malnutrition in Yemen according to UNICEF. The UN has designated Yemen as a high-level humanitarian crisis, with more than 80% of its people on the brink of famine and 10 million children are in need of urgent relief-and aid deliveries are being severely restricted. There is no end in sight to the conflict, and the UN-backed peace talks between the government and the Houthi rebels have no set date for beginning negotiations. In the meantime, 2 million Yemeni children cannot attend school, and Yemen's malnourished children risk stunting with the resultant risk of lifelong impaired cognitive functioning. "The situation continues to worsen. What we need is a political settlement urgently," says Mr Anthony Lake, UNICEF's executive director. (*Middle East Eye*, 17 Nov 2015)

• World Health Organization (WHO)

According to a WHO report, only 33 countries have raised tobacco taxes to a minimum of 75% of retail price; none among these are low- and middle-income countries (LMICs). Increasing tobacco taxes is a proven method to reduce demand and deaths from tobacco use. It could provide an innovative model for tackling the growing burden of non-communicable diseases (NCDs), which receive 1.7% of global health expenditure. On current trends, NCD funding will not reach the level required to tackle NCDs in LMICs-estimated by the WHO to be US\$ 11.4 billion. Whilst many countries channel existing tobacco revenues into health initiatives, there is a tendency for countries to focus on specific diseases, eg, HIV/AIDS. As LMICs struggle with tax collection, this underlines the need to boost their tax collection and administration capacities. (Devex, 8 Jul 2015)

According to a WHO update, no new cases of Ebola were reported in Liberia (where it had resurfaced after be-

ing declared free of Ebola in May 2015) or in recent hotspots in West Africa, where no new cases had been reported for several days. Half of the confirmed cases were from the capitals of Guinea and Sierra Leone. Contact tracing shows that almost all new cases have arisen from registered contacts of previous cases. The cases which had earlier resurfaced in Liberia were most likely caused by the re–emergence of the virus in surviving patients. The WHO noted that two new health worker infections were reported in Guinea and one from Sierra Leone. (*UN*, 22 Jul 2015)

>> The WHO is expected to recommend that all HIV–positive people should receive antiretroviral (ART) drug treatment immediately upon diagnosis. This would raise the number of people eligible for treatment to 37 million from 28 million; only 15 million people currently receive treatment. This recommendation is prompted by research which shows that starting treatment when the immune system is strong reduces the risk of death or serious health problems by 57%, and reduces the risk of transmission by 93%. The WHO is also expected to recommend ART for uninfected people at higher risk of infection, eg, sex workers. Although it is simpler to treat all HIV–positive patients rather than basing treatment on CD4 cell counts, there are challenges with managing treatment compliance at the early stage of infection, with the ensuing risk of drug resistance; the biggest challenge is ensuring that people who are infected receive treatment, as only 50% of infected people know their status. (*scidev.net*, 28 Jul 2015)

According to the WHO, two children have been paralysed in the first polio outbreak in Europe for five years. Both cases were in the Ukraine, where only 50% of children are fully immunised. The risk of the virus spreading is "high", and the WHO calls for the outbreak to be rapidly controlled. It is likely that other children have been infected without developing symptoms. The outbreak arose from the weakened strain of polio virus, which can mutate if immunisation levels are too low. The WHO recommends that everyone visiting the region is fully vaccinated, and that all residents and anyone staying for more than one month receives a polio booster. (*BBC*, 2 Sept 2015)

According to Médecins Sans Frontières (MSF), 5 million people are bitten by snakes each year, and 10% will die or suffer permanent disability. Snake bite antidotes saves thousands of people each year, but the main antidote–Fav–Afrique– is due to run out and will not be replaced in the short–term. Its manufacturer, Sanofi, stopped production in 2014 and the last batch will expire in June 2016. The technology may be transferred to another company, but this will not be completed until late 2016 and the product will not be available until late 2018. Despite the high fatality rates, snake venom antidotes have not been regarded as a priority by funders. MSF blame this situation on low awareness and lack of prioritization, and highlight that the WHO does not have a specialist in this area. (*Medical News Today*, 8 Sept 2015)

Demography

▶ After falling for 50 years, Egypt's fertility rate has risen to 3.5 children per woman. This will almost inevitably cause faster population growth as infant mortality is falling and life expectancy is increasing. The population may rise to 140 million by 2050, who will live on the 5% of Egypt's land which is habitable (along the river Nile and coastline). Egypt would be classified as "water poor" (ie, less than 1000 m³ of water per year) with a population higher than 55 million, and the country's schools and hospitals would be increasingly overburdened. Birth rates tend to fall when people grow wealthier and women are better-educated, and Egypt's rural poor have higher birth rates. The increasing number of births undermines Egypt's demographic dividend-the economic advantage of having fewer old people and children relative to the number of working adults. "Meeting the demands of this population will require strong, sustained economic growth and redistributive policies," according to Jaime Nadal Roig, head of the UN Population Fund's Egyptian section. (The Economist, 6 June 2015)

▶ By 2050, 28% of the EU's population will have reached retirement age, and the dependency ratio of over 65s to the economically-active 15-64 age group will increase from 27.8% to 50.1% by 2060. This could decrease Europe's economic growth by 0.2% per annum, and would reach crisis point when pensions become unsustainable. Europe needs to rapidly increase its younger population to ward off this crisis, and increased migration is required to fully realise this. Enabling easier immigration by refugees seeking entry to Europe from eg, Syria, Iraq and Afghanistan makes economic and humanitarian sense, as they are mainly young people who are highly motivated to work. "Refugees are our future spouses, best friends or soulmates, the drummer for the band of our children, our next colleague, Miss Iceland in 2022, the carpenter who finally finished the bathroom, the cook in the cafeteria, the computer genius or the television host," reads a petition from the Icelandic people to its government, urging more immigration. (Bloomberg, 4 Sept 2015)

▶ Tanzania has some of the lowest birth registration rates in eastern and southern Africa. 80% of Tanzanians – and more than 90% of children aged under 5 years—do not have birth certificates, according to the 2012 census. To help address this, Tanzania has launched a new system for birth registration, whereby health workers can send the baby's name, gender, date of birth and family details by phone to a central database, and a birth certificate is issued free of charge. This side–steps the obstacles of distance and cost which prevented many parents from registering births. Birth registration is essential to ensure basic rights and access to health care, education and justice. It also protects against child labour, child marriage, trafficking and military recruitment. In recognition of this, the new Sustainable Development Goals includes a commitment to universal birth registration. (*Thomson Reuters Foundation*, 13 Oct 2015)

>> China's official media announced an end to the country's 30-year-old one-child policy, reflecting growing concerns over the demographic problems of a shrinking workforce and an ageing population. This follows an easing of the policy in 2013, to allow couples who are themselves only children to have a second child. In 2012, China's working-age population decreased for the first time in several decades, raising fears that China would be the world's first country to age before it fully developed. However, only 12% of eligible couples had applied for permission to have a second child following the earlier relaxation of the policy, due to the high costs and difficulties in raising children in China. This may mean that ending the one-child rule could have limited effect on raising China's birthrate. It was announced at the end of a meeting of the Communist Party leadership, designed to formulate policies to feed into a new "5 year plan" focusing on avoiding the "middle-income trap" and move from an investment and export developing country to a "moderately prosperous society" underpinned by services, consumer spending and innovation. (Sydney Morning Herald, 20 Oct 2015)

In contrast to other age and ethnic groups-and in contrast to their counterparts in other developed countriesdeath rates amongst middle-aged, white Americans has risen. This is driven by high levels of suicide and alcoholand drug-related causes, rather than eg, heart disease and diabetes. The mortality rate for this group (white, aged 45-54 years, high-school education or less) has increased by 134 deaths per 100 000 from 1999 to 2014. Death rates for middle-aged black people, Hispanics, and younger or older people fell in the same period. Increased use of opioid drugs and higher financial pessimism are part of the factors behind the increase. However, falling household incomes amongst this group, increasing difficulty in socialising and mobility problems are other contributing factors behind rising pain levels, poor health and distress. The USA has already fallen behind other developed countries in improvements in life expectancy. (New York Times, 2 Nov 2015)

Economy

▶ On face value, China's economy seems highly innovative, as its annual spend of US\$ 200 billion on research and development is the second—highest in the world, and it leads the world in patent applications and engineering graduates. Despite the headline figures, the economic impact of innovation is more muted, with decreasing contributions to economic growth rates. This must change in order to maintain China's economic growth rates. China needs to improve innovation in customer—focused sectors, on improving efficiency; engineering new products and developing new products through the commercial application of basic scientific research. China must succeed at innovation in order to raise productivity and create high–value– added jobs–essential when wages rise and more workers migrate to the cities. (*McKinsey & Co*, Jul 2015)

Since 1990, more than 1 billion people have escaped extreme poverty (living on less than US\$ 1.25/d). However, 840 million people - 13% of the world's population still live in extreme poverty. Attention is now turning to eradicating extreme poverty by 2030. A panel convened by Brookings agree that the easier target of reducing poverty in stable, well-governed countries has been met. Attention must focus on tackling poverty in groups that may not be prioritised by their governments, and developing strategies than can work despite dysfunctional or weak governments. There are three key challenges in overcoming extreme poverty; peace, jobs and resilience. Peace is a pre-requisite and a result of poverty elimination, and people must have basic level of security in order to prosper. Jobs and sustainable incomes are essential to ending poverty; and job growth needs infrastructure, the rule of law, property rights etc. Resilience, which provides a safety net to cope with unexpected expenses or events, can be provided by eg, insurance against crop failure. Some experts note that economic growth alone cannot end extreme poverty. Ana Revanga of the World Bank calls for redistribution of wealth and equity, and also emphasised agricultural development, and access to health and education. (Brookings, 27 Jul 2015)

>> The EU, one of the world's richest and most peaceful regions, has taken far fewer of the asylum–seekers fleeing Islamic State compared to other countries such as Lebanon. The EU also compares badly to Tanzania, which has hosted hundreds of thousands of Congolese and Burundian refugees. There are strong economic grounds for Europe hosting more asylum–seekers, as well as humanitarian reasons. Europe faces an ageing labour force and high levels of government debt that future generations will struggle to repay. Migrants, including asylum–seekers, are normally

young and keen to work; this would ease the burden of an ageing population and indebtedness. Globally, migrants are net contributors with lower crime rates and higher likelihoods of starting businesses. And if labour markets reforms make it easier for migrants to work, it will support closer integration and make it less likely that young unemployed men are attracted to extremist groups. Europe could emulate the USA's economic success which was built on earlier immigration. The message is: let them in – and let them earn. (*The Economist*, 29 Aug 2015)

>> The IMF warned that the economic slowdown in emerging markets is affecting global economic growth, which is at its lowest level since the financial crisis. There is an increasing risk of a global recession, and the IMF revised its estimate for 2015 global economic growth downwards, from 3.3% to 3.1%. It also cut its estimate for 2016 to 3.6%. Investors are pulling out funds from emerging markets, and it is estimated that 2015 will see the first net capital exodus for 27 years, with more than US\$ 1 trillion leaving countries like Brazil, Turkey and South Africa. Although China's booming service sector off-sets its slowing manufacturing sector, there are external negative effects on global commodities suppliers which are reliant on Chinese markets. The outlook is worsened by emerging economies' increased debt levels - often in US dollars, and hence more vulnerable to rising US interest rates - and higher default risk. In response, the IMF has called for the US Federal Reserve to delay its planned rise in interest rate, for Europe to deal with its trillions of US dollars of bad debt, and for emerging markets to overhaul their economies and strengthen their resistance to financial risk. (Wall Street Journal, 8 Oct 2015)

▶ Sub–Saharan Africa is home to many of the world's fastest–growing economies, with increasing interest from international private equity investors seeking to benefit from the continent's economic growth and emerging middle– class consumers. A report from the UK's Overseas Development Institute (ODI), shows that this investment has grown 500% since 2008 and accounts for US\$ 12 billion – or 20%–of annual cross–border investments. Capital flow is essential for economic development, but the continent still suffers from a lack of investment opportunities, with firms often being too small and lacking in human capital. The ODI calls for development finance institutions to support the creation of more medium–sized businesses, and to provide investors with less costly and more flexible risk insurance tools. (*Reuters*, 8 Oct 2015)

Energy

According to the World Bank, power shortages reduce economic growth by up to 4% each year in sub-Saharan Africa, with many businesses forced to rely on expensive generators. Poorer people are disproportionately affected, as they spend up to 16% of income on energy, and use expensive kerosene or batteries for cooking and light. The capacity installed by independent power producers in Africa has grown by 14% each year since 1992-and an everincreasing share is going to renewable energy. This is partly because Africa has some of the world's best untapped resources for renewable energy (eg, rivers and hot deserts), and renewable energy sources can be set up quickly and cheaply to meet shortages. It is easier to connect remote villages to a local renewable energy source than a main grid. With falling equipment prices, and the right regulatory environment and access to finance, Africa could become a leading producer of clean energy - making it richer and greener. (The Economist, 6 June 2015)

>> In the past decade, more than US\$ 2 trillion has been invested in renewable energy. According to the International Energy Authority, cumulative investment in low-carbon energy supply and energy efficiency must reach US\$ 53 trillion by 2035 to keep global warming within the 2°C safety limit. This figure sounds daunting, but it is only 10% higher than the energy investment required (US\$ 53 trillion) to keep apace with economic and population growth. The price difference between conventional and renewable energy is narrowing, and clean energy could support the transition to a low-carbon economy and meeting economic and development goals. However, national governments' local content requirements (LCRs), which normally require solar or wind power developers to source a given percentage of jobs, supplies or resources locally are hindering international investment in these energy sources. LCRs increase the cost of intermediate inputs, and lead to less competition, therefore deterring investment. The OECD calls for multi-lateral cooperation to address these barriers to trade and investment in clean energy. (OECD, 9 June 2015)

▶ Since 2012, Iran's government has pushed renewable energy as an alternative to fossil fuels, which currently supply 94% of its electricity. Energy developers are building wind turbines on ridges, and Iran aims to install 5 gigawatts of renewable energy capacity by 2020, making it comparable to France and the UK. The prospect of sanctions being lifted after the signing of the nuclear deal on 14 July has led to increased interest in all energy developments, with oil companies keen to exploit Iran's oil fields, which need an estimated US\$ 200 billion of investment. Banks are also willing to start lending again, once payment systems are restored and sanctions are lifted. However, some developers are pushing ahead with financing, such as Umwelftconsult, who are seeking US\$ 44 million for the installation of wind turbines to generate 47.3 megawatts of electricity – and more will follow. (*bloomberg.com*, 30 Jul 2015)

>> The oil and gas company Statoil will build the world's largest floating offshore windfarm, off the northeastern coast of Scotland. The project (Hywind Scotland) differs from conventional offshore windfarms by using turbines attached to the seabed by a mooring spread and anchoring system, and could power nearly 20000 homes. Floating wind farms may reduce generating costs for offshore developments to under US\$ 150MWh, with larger projects reducing costs to US\$ 130-140MWh. Currently, the average global price is US\$ 170MWh. A report from the Energy Technologies Institute (ETI) suggests that offshore wind could be a cost-effective form of low-carbon energy for the UK by 2025. Ms Irene Rummelhoff, Statoil's VP for new energy solutions says "floating wind represents a new, significant and increasingly competitive renewable energy source. Statoil's objective with developing this pilot park is to demonstrate a commercial, utility-scale floating wind solution, to further increase the global market potential." (The Guardian, 2 Nov 2015)

>> South Africa proposes to build 8 new nuclear power stations, at a cost of R1 trillion (US\$ 72 billion). Expanding South Africa's energy capacity is essential for economic growth and housing development, and the country suffers from power outages and ageing infrastructure. South Africa, like other countries after the Fukushima nuclear disaster, had considered delaying the expansion of its nuclear energy capacity. However, the government appears to have climbed down over this policy, with its surprise announcement of a large deal to build new nuclear power stations, with Russia as the preferred supplier. This move is subject to intense criticism over its speed and lack of transparency, and there has been allegations of corruption. There is scope for covering the country's energy shortfall by increased investment in renewable energy and energy saving strategies. (theconversation.com, 5 Nov 2015)

Environment

▶ Irrigation and the increased watering of fields in sub–Saharan Africa are creating conditions ideal for invasive plant pests, such as the tomato leaf miner. This moth attacks crops like tomatoes, potatoes, peppers, aubergines and tobacco. This insect is native to South America, but spread to Africa via Europe. East Africa is particularly vulnerable, as increased rainfall and temperatures as a result of climate change-combined with irrigation - creates warm and damp environments ideal for crop-eating insects from tropical climates. According to Dan Bebber from the University of Exeter, UK, this poses dangers for food production. "Irrigation could trigger changing pest distributions by allowing a host plant to grow where it would not otherwise growth, and by producing conditions for the pest or pathogen to grow. Also, pathogens can be spread around in irrigation water on a small scale." The International Maize and Wheat Improvement Center in Kenya is trying to alleviate the problem by training farmers to introduce natural predators to manage the pest. (scidev.net, 13 Aug 2015)

▶ In 2010, Brazil passed a law which required all that solid waste be deposited in modern landfills, lined to prevent toxins from soaking into the soil. This has failed to stop rubbish being dumped unsafely, caused by a shortage of money and the political will to enforce legislation. The problem of unsafe dumping is worse in poorer areas with fewer landfill sites and less money. 60% of Brazil's municipalities failed to meet these requirements, but none have been sanctioned. Moreover, the federal district around Brazil's capital city, Brasilia, continues to dump its waste in unregulated sites 15km from the city centre. Fortunately, the main transport routes used by the country's law–makers in the capital remain pristine. (*The Economist*, 15 Aug 2015)

▶ Vietnam is increasingly reliant on coal-fired electricity, with demand growing at one of the highest rates in South– east Asia, supporting one of the world's fastest–growing economies. Demand is predicted to grow by 10–20% each year up to 2030, and 50% of energy will be generated by coal by 2020 – currently 33%. This has serious implications for air quality, and the WHO has linked air pollution from solid fuels to 3.7 million deaths – 70% in Asia and the Pacific region. Vietnamese mines or coal power stations do not take account of climate change or related extreme weather, and recently 17 people died in floods in north– eastern Vietnam which were linked to extreme weather events. "This is the first environmental disaster in Vietnam's coal–mining industry, and the consequences are yet to be identified in terms of scale, duration and intensity. It's time for Vietnam to evaluate comprehensively the national energy security related to power sources," says Nguyen Dang Anh Thi, of the World Bank's International Finance Corp's resources efficiency programme. (*bloomberg.com*, 17 Aug 2015)

▶ Indonesia's forest and peatland fires have killed at least 19 people, and 500 000 people have suffered from severe respiratory illnesses from the resulting haze. Across Southeast Asia, an estimated 110 000 people die each year from smoked caused by forest fires, mainly due to heart and lung problems. These fires are a man-made crisis, with most danger spots arising from oil palm and pulp wood plantations. The current haze is largely arising from dry and deforested peatland, as peat swamps are naturally resistance to fire, but are highly flammable when they are dried out and degraded. In response, President Joko Widodo has instructed the Forestry and Environment Ministry not to issue new permits for peatland monoculture cultivation, and to restore damaged peatland and review all existing peatland licences. (*Jakarta Post*, 1 Nov 2015)

French economists Lucas Chancel and Thomas Piketty have proposed a global US\$ 196 levy on business class air tickets, and US\$ 21 to raise US\$ 150 billion needed each year for climate adaptation. Currently, according to the OECD only 16% of climate finance is targeted at adaptation – the remainder funds low carbon projects. This proposal would use air travel as a proxy for affluence across countries, as the wealthiest elite in developing countries are beginning to outstrip working–class Europeans in carbon emissions. There are huge disparities in carbon footprints, with 10% of people being responsible for 45% of global emissions. "Taxing flights is one way to target high–emitting lifestyles, especially if we tax business class more than economy class," says Lucas Chancel. (*Climate Change News*, 5 Nov 2015)

Food, Water and Sanitation

>> 25% of the world's food is wasted due to inefficient harvesting, inadequate storage and domestic wastage. If this were halved, an additional billion people could be fed-particularly crucial when 1-in-9 people (795 million in total) go hungry each day. In developing countries most wastage occurs at the production and storage stages. A lack of infrastructure is part of the problem – eg, inadequate roads make it harder for farmers to sell their surplus, and more reliable electricity supplies would enable grains to be dried and vegetables to be kept cool. It would cost an estimated US\$ 239 billion to halve post-harvest losses in the developing world by investing in infrastructure, generating US\$ 3 trillion of benefits. This would make food more affordable, and 57 million people would no longer be at risk of hunger. However, investing in improved food production, targeted at the major food crops and including small farmers would engender greater benefits. An additional US\$ 88 billion investment each year would increasing yields by 0.4% - giving additional benefits of US\$ 3 trillion. (The Guardian, 24 Jun 2015)

▶ A study published in *PLoS Medicine* suggests that pregnant women who defecate in the open are more likely to have a premature delivery or give birth to a baby with low weight than those who use toilets. India has the highest number of premature births in the world at 3.5 million (followed by China at 1.17 million), and nearly half of India's population defecate in the open. Premature births and low birthweight are linked to health problems up to adulthood, including diabetes, hypertension and depression. The study also concluded that higher levels of education are associated with reduced risks of adverse pregnancy outcomes. India's Prime Minister, Narendra Modi, has pledged to improve India's sanitation, and wants every home to have a toilet by 2019. (*BBC*, 8 Jul 2015)

▶ 2.1 billion people – 30% of the world's population – are overweight. This is double the number in 1980, and more than 2.5 times higher than the number of chronically–hungry people. According to a report by the McKinsey Global Institute, being overweight or obese is linked to 2.8 million deaths annually due to conditions like diabetes, cancer and cardiovascular disease. Developing countries have 30% more overweight and obese children compared to developed countries. It estimates the annual cost as US\$ 2 trillion – 2.8% of global GDP. In light of this, the WHO cuts its recommendation for sugar consumption from 10% to 5% of adult daily calories. The report offers several other recommendations, eg, smaller fast–food portions, advertising restrictions, better nutritional information, reformulating processed foods, more exercise at school, and healthier meals in the workplace and school. These interventions, although difficult to achieve, do work; this is shown by the 43% decrease in childhood obesity in the USA in the past 10 years. (*Project Syndicate*, 20 Jul 2015)

>> According to the latest Global Hunger Index despite population growth, deaths from large-scale hunger have fallen from 1.4 million in 1970 to 40000 a year since 2000. This is accompanied by hunger levels falling by 30% since 2000. However, hunger is still a critical issues, with 800 million people being chronically undernourished. The Index also shows countries with the most improved records in fighting hunger (eg, Ukraine, Brazil and Mongolia), and the least improved, eg, Chad and Iraq. China has witnessed spectacular improvements in food security, changing from having 50% of the world's deaths from famine to none. There are several countries with "alarming" hunger levels, including those experiencing conflict and epidemics which undermine food security. The UN's Food and Agricultural Organization also notes the difficulties in generating estimates for countries with unreliable data, and are trying to monitor food security with measures that are less reliant on government stability, noting that deliberate starvation is still used as a tactic of war. (NPR Goats and Soda, 16 Oct 2015)

The aid agency Goal warns that Ethiopia is facing its worst drought in decades, and more than 8 million people are in need of food assistance. This is greater than the 2011 drought in the Horn of Africa, which claimed 200000 lives in Somalia. More than 80% of Ethiopia's people work in agriculture, rendering the country particularly vulnerable to drought and climate change, and food prices are already increasing. The UN Office for the Co-ordination of Humanitarian Affairs (OCHA) estimates that 15 million people will need food assistance-more than Syria-350000 people will suffer from severe acute malnutrition, 450 000 livestock deaths which would destroy livelihoods and increase food insecurity; and 1.8 million people would be affected by drinking water shortages. The Ethiopian government has diverted US\$ 200 million from infrastructure expenditure into food supplies, and has appealed for funds. The OCHA estimates that US\$ 451 million will be required. "The concern is that if there is not a timely response the situation will deteriorate," says John Rynne, Goal's director in Ethiopia. (Irish Times, 30 Oct 2015)

Peace and Human Rights

>> The World Justice Project's index on corruption and justice, which measures the rule of law in 102 countries, is based on responses from 1000 citizens in each country. Its indicators are: constraints on government power; absence of corruption; open government; fundamental rights; order and security; regulatory enforcement; civil justice; criminal justice; and informal justice. It ranks Denmark at the least corrupt country, and Venezuela as the most corrupt. The results will inform discussion on the post–2015 development agenda, which emphasises good governance and rule of law as underpinning economic and social progress. The sustainable development goals will include commitments to promoting the rule of law, ensuring access to justice, end corruption, and ensure transparent and accountable institutions. (*The Guardian*, 2 Jun 2015)

Myanmar's Muslim Rohingya population have been described as"the most persecuted minority in the world". They cannot claim citizenship in Myanmar, or other countries. They are fleeing repression and brutality in Myanmar, with an estimated 100000 Rohingyas estimated to be in Malaysia (where they have no legal status and forbidden to work), and hundreds of thousands have thought to have fled to Bangladesh (where, in an UN-supervised operation, 200000 Rohingyas were brutally repatriated in the 1990s). In Myanmar, no-one has faced prosecution or imprisonment for the attacks and murders on the Rohingya population in 2012. Human rights campaigners warn that they are "at grave risk of additional mass atrocities and even genocide", noting that some of the pre-conditions of genocide (stigmatisation, harassment, isolation and the weakening of civil rights) are already in place. (The Economist, 13 June 2015)

▶ Nine Islamic countries have stoning as a judicial sentence, and five have amputation as judicial sentences. This is despite Islam's sacred texts prescribing less harsh punishments than Judaism or Christianity, and allowing for the forgiveness, and hence sparing, of murderers. Under the Ottoman empire, one person was stoned to death in 600 years, but since the 1970s ever-harsher punishments have been introduced, with Iran, Pakistan and Afghanistan implementing sharia law. Islamic law definitions are being stretched to include homosexuality and apostasy as punishable offences. This is possible because Islamic law does not rely solely on the Koran as a law source, but includes the recorded sayings and actions of the Prophet Muhammad. However, the main reason is the instability of the Islamic world, where punishments can be used to target opposition groups, and placate hardline clerics or public opinion. Even when punishments are eased (eg, stoning in Iran), this tends to be via moratorium rather than abolition. Liberal lawyers in Saudi Arabia are campaigning for penalties to be codified to prevent harsher sentences when alternatives are available, although the fact that the regime's jurisprudence says that lashes, stoning and the death penalty are necessary is inescapable. (*The Economist*, 4 Jul 2015)

>> Amnesty International, the human rights campaigning group, has voted to support a policy that calls for the full decriminalisation of all aspects of consensual sex work. This was in the face of intensive lobbying from opponents who are opposed to exempting buyers and managers from penalties. Amnesty International argues that decriminalisation is the best way to reduce risk for sex workers, who can face arbitrary arrest and detention, extortion, harassment, and physical and sexual violence. Following the vote, Amnesty International will develop a final policy that can be used to lobby governments to repeal most laws that forbid the sale and purchase of sex. However, Amnesty International does not plan to have a major, global campaign on decriminalisation. Instead, national branches will take forward their own campaigns. (New *York Times*, 11 Aug 2015)

▶ Tunisia's National Dialogue Quartet – a coalition of union leaders, business people, lawyers and human rights activities—won the 2015 Nobel Peace Prize for "its decisive contribution to the building of a pluralistic democracy in Tunisia in the wake of the Jasmine Revolution of 2011." Tunisia's transition to democracy has been a sign of hope amongst the other failures of the Arab Spring, with the quartet underpinning the Ennahda—led Islamic government's willing cessation of power. Although peace in Tunisia is still fragile, the president of the Human Rights League, Abdessattar Ben Moussa said that winning the Nobel Peace Prize "proves that dialogue is the only way to solve a crisis, and not weapons." (*New York Times*, 10 Oct 2015)

Science and Technology

>> Cambodia's traditional diet of rice and fish is low in iron, which leaves many people at risk of iron deficiency and hence anaemia. Christopher Charles, a medical student at McMaster University in Canada, has designed a simple solution that could provide 75% of daily iron needs. He designed a small iron fish, to be placed in a litre of water and boiled for 10 minutes with some citrus to aid iron absorption. The resulting iron–rich water can be used for drinking or cookery. The idea was inspired by iron leaching into food from iron–based cooking pans – the fish is a substitute for these pans which are unsuitable for most Cambodian people. Christopher's iron fish won the Grand Prix for product design at France's Cannes Lions International Festival of Creativity. (*slate.com*, 29 June 2015)

According to a study published in *The Lancet Psychiatry*, daily tobacco smokers may be at increased risk of psychosis. It found that 57% of people with their first episode of psychosis are smokers - nearly 3 times higher than the general population. This high rate has long been recognised, but it was generally believed that people used tobacco to alleviate the distressing symptoms of psychosis and possibly the side-effects of anti-psychotic drugs. However, tobacco may have a causal effect, which is consistent with excess dopamine causing psychotic illnesses - and nicotine exposure increases dopamine levels. The exact relationship is more subtle, as people tend to inherit vulnerability to developing schizophrenia, and other factors will increase the risk. Prof Michael Owen of the Institute of Psychological Medicine and Clinical Neurosciences at Cardiff University hopes that further genetic research will establish the relationship, noting that "the fact is that it is very hard to prove causation without a randomised trial, but there are plenty of good reasons already for targeting public health measures very energetically at the mentally ill." (The Guardian, 10 July 2015)

▶ Results from a UK study published in *The Lancet Neurology* suggests that the risk of developing dementia is now declining. This balances the increasing number of people living into their 80s and 90s, so that the overall number of people with dementia remains reasonably stable. This potential decline may be caused by improved physical health– linked to better nutrition and less infectious diseases; improved cardiovascular health which has a protective effect on brain health; and increasing levels of mental stimulation. Interventions to promote general health may be more effective that wide—scale screening for dementia, partly because existing tests can be unreliable and add little to treatment options. However, the UK's Alzheimer Society highlight that the results could be overturned by other trends, eg, increasing rates of obesity and diabetes. (*New Scientist*, 21 Aug 2015)

William C Campbell, Satoshi Ōmura and Youyou Tu won the 2015 Nobel Prize in Physiology or Medicine for their work in developing therapies against parasitic infections. Campbell and Ōmura discovered a class of compounds (avermectins) which kill parasitic roundworms which cause infections such as river blindness and lympathic filariasis. Tu, the first China–based scientist to win a science Nobel, developed the anti–malarial drug artemisinin. Stephen Ward of the Liverpool School of Tropical Medicine says that these awards highlight the global acceptance of the importance of parasitic infections, and neglected tropical diseases, noting that artemisinin has saved "millions" of lives, and that avermectins have protected millions from parasitic roundworms. Each year, Merck donates 270 million treatments of avermectin. (*Nature*, 5 Oct 2015)

>> As Swaziland is poised to become the first malaria–free country in sub-Saharan Africa, the world should aim beyond controlling infectious diseases, and look towards the eradication of certain diseases. Measles, mumps, rubella, filariasis, pork tapeworm, malaria and hepatitis C are plausible targets; eliminating them would save 1.2 million lives each year-and transform many millions more. Mass vaccination campaigns can decrease disease levels, but parasites evolve resistance, and funding may dry up when political attention turns elsewhere-causing diseases to bounce back. Improved communications that support monitoring disease outbreaks; better medical technology in the form of drug innovations; and genetic engineering's potential all make eradication more achievable. The emergence of HIV/ AIDS and Ebola has also galvanised political will and led to improved health infrastructure. Candidates for eradication will change over time; and HIV, one of the biggest prizes, shares with smallpox the vulnerability of human-only hosts and the inability to survive independently. (The Economist, 10 Oct 2015)

KIRSTIE-ANN McPHERSON: MY PERSONAL EXPERIENCE AS A WHO INTERN

For my internship, I spent 6 weeks living in Geneva, working in the Child and Maternal Health department the World Health Organization (WHO) headquarters. I found the experience to be hugely enjoyable, and a great learning experience in both an academic and personal sense.

Arriving at the WHO was a daunting experience as this was the first time I was exposed to such a large international organisation. For a young person starting out in the global health world, entering a building where so many world– leading experts work is exciting and scary in equal measures. However, I soon settled with the help of my supervisor. I found the environment to be welcoming and relaxed, and I was able to get to know many of the people working around me. Every person I asked found time to explain their interests and current projects to me, including the director of the nutrition for health and development department who I had a discussion with about governance of the global food industry, an area of personal interest.

As well as gaining an insight into the breadth of work of various experts at the WHO, I was able to develop a host of my own skills by undertaking my own work and assisting others. My project was focused on evaluating the effectiveness of the CHNRI heath research prioritisation methodology. This systematic method was developed from 2005-2008 and aims to determine global health research priorities in a fairer and more transparent manner with a view to filling the knowledge gaps that result in child mortality remaining high. It features crowd sourcing of expert opinion to establish consensus over research questions of high priority. The main work I did on this topic built on that of a previous intern from the University of Edinburgh. It was based on searches of academic literature relating to the priorities identified in CHNRI exercises about 5 different child health topics: neonatal infection, low birthweight/prematurity, childhood diarrhoea, childhood pneumonia and intrapartum-related neonatal death. We began to determine the interest in these topics in the 3 years' previous to the publication of these CHNRI exercises, using the number of relevant papers published as a quantitative measure. The comparison value was the numbers published in the years post publication and 3 years of lag time to allow time for studies inspired by the published priorities to be conducted. This was an interesting project, which developed my academic searching skills as well as my critical thinking in relation to developing a method to measure and evaluate an intangible concept like the dissemination of ideas.



Photo: Kirstie-Ann McPherson at the World Health Organisation

I also spent time in the department facilitating the AMAN-HI study looking at the global causes of maternal and newborn deaths. Taking part in some of the groundwork of the study accrediting local physicians to perform verbal autopsy highlighted to me the scale of the work involved in performing the research that goes on at the WHO. These projects take years to design and perform, and spending hours working through a small part of this put into perspective the skill and patience of the people working at the WHO gathering and sorting complex data from across the world. For me, this further highlighted the importance of the WHO as a centre point in the field of global health, in this case coordinating in–country field work with that of experts across the world.

My time in Geneva was not only filled with work however, and the intern community at the WHO was part of making my experience so valuable. There are 300 interns at peak time in summer (none of whom are paid) meaning there is a near constant stream of talks and social events to distract you from working! Spending summer in the heart of Europe was also fantastic as it gave us the opportunity to travel and make the most of every weekend, taking in Lake Annecy, Yvoire, Sciez, Cannes, Lucern and Bern in my time there. However the highlight of my free time was definitely paragliding from the top of Mont Salčve and seeing the beautiful of Geneva from the sky as the sun set. Overall, I had an inspiring time being submerged in the world of global health for a few short weeks and I am more than grateful to the EUGHS for helping me get the opportunity to experience work and life at the WHO HQ.

KENNETH McLEAN: MY PERSONAL EXPERIENCE AS A WHO INTERN

I returned to my 3rd year of undergraduate medicine following the completion of an intercalated degree in Epidemiology at the University of Edinburgh. I was enthused to continue to explore my newfound interest in global health and build upon the knowledge and skills I had gained as part of the course. This culminated in the incredible opportunity this summer to undertake a six week internship in the Public Health, Innovation, and Intellectual Property (PHI) Unit of the World Health Organization, Geneva. While there, I was supervised by Erin Sparrow, an experienced technical officer working on influenza virus vaccination, who immediately helped me to feel a welcome and valuable member of the team.

The main focus of my internship was to construct and deliver a survey of vaccine manufacturers to establish the current global influenza vaccine production capacity. This was in preparation for the Third WHO Consultation on Global Action Plan for Influenza Vaccines (GAP III) taking place in November 2016. These successive programmes have aimed to address the shortage of influenza vaccines for seasonal epidemics and pandemic influenza through encouraging seasonal vaccine uptake; expanding the vaccine production capacity; and promoting further vaccine research and development (R&D). Although it was a bit daunting to be trusted with such a task, I was excited to contribute to a programme that aims to address this critical global public health issue. In addition, I assisted in the scientific and ethical review, and cost analysis of WHO-supported clinical trials of influenza vaccines being developed within low- and middle-income countries. This was a valuable chance to utilise and develop the knowledge and skills I gained though my medical and epidemiological backgrounds in a real world context. I certainly gained a new appreciation for the practicalities and processes in conducting these clinical trials in an ethical and effective manner.

It was a very exciting time during my placement at the PHI unit. My first day was spent observing the Ebola Research and Development Summit where I rapidly gained insight into the many successes, challenges, and lessons learned from the West African Ebola crisis. It immediately helped to highlight how great a privilege my internship was. I was actually at the epicentre of global public health policy development and implementation, and gaining a first-hand understanding of this process. I was also thrilled to be present for the 68th World Health Assembly (WHA), held at the Palais des Nations. This was the first WHA following the catastrophic Ebola outbreak. Therefore, the focus was on the need to build more resilient health systems; improve preparedness and response to emerging outbreaks; and increase R&D on neglected tropical diseases (NTDs). I found it a humbling experience to observe thousands of international delegates and non-governmental organizations (NGO) representatives gathered together in the spirit of collaboration. It was incredible to observe and participate in discussions on some of the most urgent and important health issues facing the world today-the post-2015 sustainable development goals; the health impact of climate change; antimicrobial resistance; pandemic influenza; and equitable access to effective pharmaceuticals.

Alongside the work I undertook, I had the chance to expand my global health horizons though attendance at WHO seminars and workshops, and to be part of the vi-



Photo: Kenneth McLean inside the UN

brant intern community. While there, I was able to meet with many others who all shared a common aspiration to act to enhance global health. It was fantastic to be able to exchange experiences and perspectives, and to learn from people from an array of professions and places the world over.

As with all good things, my internship sadly had to come to an end. My sincere thanks must go to the Edinburgh University Global Health Society (EUGHS) for their generous financial support, and to my dissertation supervisors – Professor Harry Campbell and Dr Harish Nair – who provided the opportunities and encouragement that enabled me to pursue this internship. Finally, I am immensely grateful to Erin Sparrow and everyone in the Influenza team for such a fantastic chance to work with them, and for the supportive and engaging environment they provided. It was an incredible and unforgettable experience which has only served to further sharpen my interest in global health. It will undoubtedly shape the course of my future medical career.

MIA COKLJAT: THE HEADQUARTERS OF WORLD HEALTH – WHAT DIFFERENCE CAN A NAÏVE INTERN MAKE?

Summer of 2015 saw my internship at the World Health Organization (WHO) in Geneva. The WHO is divided into headquarters and six regional offices. The headqauarters themselves are then divided into smaller departments that focus on different aspects of health, such as maternal and child health, or non–communicable diseases etc. I was based within the Health Statistics and Information Systems branch of the larger Health Systems and Innovation department.

Whilst there, I was to work on a scoping review, to be published in parallel with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER).

It is possible for us to generate health estimates across all countries. Such estimates, termed health metrics, include: mortality, prevalence, and incidence of different diseases or factors that contribute to disease (such as smoking). Together this is termed global burdens of disease (GBD). We can use GBD to create a larger, more global picture of what is making people ill, how ill, and where, and how this is changing. Depending on where these burdens of disease are, the greatest allow us allocate resources appropriately; therefore the generation of health metrics can influence health policy. Additionally, they allow us to monitor the impact of worldwide goals, such as the Millennium Development Goals (MDGs).

In order to make these estimates however, we have to use many different data sources. This includes high–quality vital registration data in developed countries, but also low quality self–reported data with significant data gaps in other countries. Moreover, for a given disease for example, there are variations in populations studied, what the outcome measures were, and what methodology was used to collect the data. It is possible to adjust for this by using statistical models; however the more data inputs there are, the more complicated these models become. This can then involve steps such as data cleaning, data pre-processing, data adjustments and weighting of data sources, as well as the mathematical formula itself and the statistical code used. Therefore straight away we can see that unless each step in this complex process is described transparently, there is space for data manipulation, therefore leading to unreplicable health estimates.

Hence, as soon as we are unsure of the source of data, or what all the components of the statistical model are, we begin to be unsure about whether the methodology is transparent. Therefore the health estimate cannot be relied on. Since we use these health estimates to influence our policies and determine our resource allocation, it is of paramount importance that they are replicable . For this reason, we need guidelines that outline a list of basic requirements required in every publication; their inclusion allow us to be sure of the quality and transparency of the health estimate that is reported.

It is possible that all the components outlined on the checklist are already being done, rendering the guidelines surplus to good practice; conversely it is also possible that none of components are being outlined, making the guidelines unrealistic. Therefore my role was to create a scoping review of studies making estimates relating to global burden of disease, and assess them for the current state of reporting.

However, there are wider ideas about global health to learn at the WHO. Within the global health world, there is a relatively new–found favour of community–based interventions. This refers to the idea of using the community as a "setting" and a "resource" for a particular intervention [4], there to be utilised. This is the idea of taking health care back to local environment of the patient; whether it is management of mental health, or providing rehabilitation after severe acute illness such as cardiac rehabilitation. Thus community–based interventions use a *behavioural change*



Photo: Mia Cokljat at the WHO

of the patients themselves to reduce overall population risk of a certain morbidity. There is not necessarily a need to institutionalise patients. The latter takes up vast resources and are not necessarily cost—effect and drastically disrupts the daily lives of patient; moreover it is important to remember that a burden of disease affects the entire community. This is starting to be recognised at a global policy making level. Unfortunately, doctors are biased to the individual in front of them, and therefore a third party is imperative (such as the WHO) to act as governing body to allocate resources to the community—based interventions, create frameworks describing these interventions, and generate cost–effective policies. The aim of this is to improve the quality of life for the greatest number of people worldwide; this is the utilitarian approach to health care.

It has been suggested by models of community-based interventions, that the intervention "starts where the people are". What this means is that rather than creating completely brand new external resources, we see what already exists within the community and modify the already existent practice. Positively, small pilot trials hinted at the optimisation of interventions if they were to be available in one's own community. This includes perinatal care and injuries as a result of alcohol misuse. However despite this initial promise, there appears to be little progress in creating strong community support system, with only a moderate improvement of health burdens as a result. It would seem the best intentions of the frameworks and guidelines of the WHO, these theoretical ideas do not translate down to feasible actions by health practitioners, and "penetrate" the community. Therefore there are barriers between policies and action; but what these barriers are, we do not know. It could be because there is a lack of education of community-based practitioners on how to technically approach ill health in the community. It could also be, as is the case with mental health, there is that the stigma and lack of awareness of illness means that community interventions are simply not accessible to those that need it. It is also possibly that simply, the interventions are just not be being used for long enough.

Whilst this is an oversimplification of the ideas currently surrounding barriers to implementation of global health interventions at a community–level, it is worth leaving future interns with a thought. It may be that we as interns are too caught up in the large, philosophical questions of global health; instead of asking what needs doing by someone else, we need to ask *how is it* that we can do it. By asking this, we can determine what actions specifically allow us to cross the breach between policy and quantifiable change.

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Providing nursing care to Ebola virus disease patients: China Ebola Treatment Unit experience

VIEWPOINTS

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• ince the outbreak of Ebola Virus Disease (EVD) in mid 2014, many countries and WHO sent physicians and nurses to sub–Saharan Africa. The Chinese government sent three groups of medical staff to Liberia over the period from 14 November 2014 to 15 May 2015 and built an EVD treatment unit located in the Samuel Kanyon Doe (SKD) sports stadium of Paynesville which then received patients from across the country. EVD is a highly contagious and lethal disease [1] with no effective vaccine or specific treatment regimen. Since the beginning of 2014, Ebola virus has infected more than 20000 people and killed more than 7000 patients. WHO reported that infected medical staff are one of the groups with the highest case fatality ratios. The President of People's Republic of China issued an order to "cure EVD patients, as many as possible, while keeping zero infection of medical staff." With this goal, the Ministry of Health organized a panel of infectious disease prevention and treatment experts to design the Ebola Treatment Unit (ETU) in Paynesville, Liberia, and sent 3 medical teams (approximately 700 physicians and nurses) to Sierra Leone and Liberia.

The Ministry of Health designed a curriculum for ETU staff, which included: geographic and cultural orientation to West Africa, the peace keeping tasks of United Nation in Africa, contagious disease prevention and treatment in tropical zones and the use of personal protective equipment (PPE). Staff were trained in PPE dressing and undressing in simulation training centers in military medical universities and general hospitals in different regions. Regularly rehearsed patient scenarios in high ambient temperatures were an essential element of the training to ensure staff experienced some of the real life challenges of patient care in these settings.

Physicians and nurses in China in the ETU had prior training and at least 5 years of experience in epidemiology and infectious disease, respiratory, anesthesiology, general sur-

Principle of "Extreme Caution" is never to be underestimated in order to reach the "Zero Infection" goal among medical and nursing staff. Ebola virus disease is not a "horrible monsters" if medical and nursing staff strictly follow personal protection principles.

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gery and clinical nursing. Most of them were directors and head nurses in tertiary hospitals affiliated to Military Medical Universities or General Hospitals throughout China. The physician nurse ratio was 1:1.5 and 79% of nurses had more than 10 years of experience. Their age ranged from 24 to 58 years and most of them had participated in medical rescue missions following earthquake or flood disasters or had experience in sports injury treatment at large international events such as the Olympic and World Expo Games.

The China ETU comprised an outpatient clinic, observation ward, treatment ward, infection control and an anti– epidemic department. A group of supervisors were responsible for the surveillance of infection control quality. **Figure 1** is a simplified diagram of the layout of the contaminated (in red color), semi–contaminated (in yellow color) and uncontaminated (in green color) areas of the ETU.

Within the wards of observation and treatment, there were strictly designed entering and exiting routes in order to avoid cross infection (**Figure 2**). This was arranged as a

one–way system. Patients were only allowed to have daily activities in the patient's room and exterior corridor and not allowed to enter the inner corridors which were staff–only areas. The area in red was considered as a contaminated area (colour intensity proportion to the hypothetical virus density). All the items of PPE were disposed of in dressing room 1 and dressing room 2 except water–proof boots in dressing room 1. Used boots were collected by sterilization and supply nurses after disinfecting them with 5000 mg/L chlorine solution, drying with sunshine, checking leakage with a flashlight in the dark. They were then sent to dressing room 1 as required.

By the end of 2014, researchers, caregivers and the support team at the ETU went through the "lived experience" of preparing and caring for patients with exposure as well as confirmed cases. Appropriate PPE dressing and undressing protocols were developed:

Dressing room 1: Wearing of split gowns with disposable socks, latex gloves, N_{95} mask, head cloth, goggle, conjunctive protective gown, suitable butyronitrile gloves, surgical

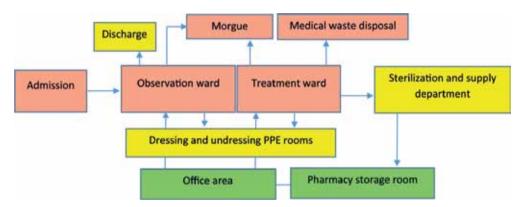


Figure 1. Structure map of the Ebola Treatment Unit (ETU).

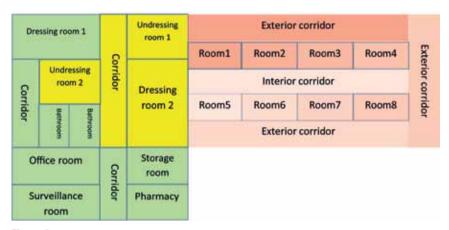


Figure 2. Architectural structure of observation or treatment ward in the Ebola Treatment Unit (ETU).

cap, and waterproof boots sequentially (checking correct size by making extended motions);

Dressing room 2: Hand washing, taking on disposable surgical gown, facial splash shield, latex gloves, boot covers, and before entering the patient's room wearing the outermost layer's gloves;

Undressing room 1: Hand washing, taking off and then putting on gloves; splashing chlorine disinfection solution from head to feet; washing hands and taking off the disposable surgical gowns; taking off boots covers, gloves, facial splash shield, cap, and washing hands; entering the chlorine solution pool to disinfect boots for 2 minutes;

Undressing room 2: Opening the door with paper tissues; entering the dry pool to take off boots, using an instrument to transfer boots into recycle



Photo: Nurse Chu Danfeng, Feng Li and Chen Dan, accompanying to Medical director Li Fuxiang of China ETU, are treating and caring for Ebola patient in the ward. (Courtesy of Cao Jie)

bucket, changing slippers; washing hands and taking off protective gown; washing hands and taking off butyronitrile gloves; taking off goggle and head cloth; washing hands and taking off gloves; taking off mask with naked hands and then washing hands and entering the shower room.

From 15 December 2014 to 20 March 2015, there were 296 patients screened at the outpatient clinics, 56 of whom were admitted to the observation ward and 11 diagnosed with EVD by Ebola PCR laboratory examination. The average age of confirmed cases was 42.3 years old; 7 were male and 4 were female. According to the common symptoms listed by Dr Jarrett [2], 100% had the symptom of weakness, 90.9% had fever >38.6?C, 81.8% had diarrhea, 72.7% had vomiting, 72.7% had muscle or joint pains, 63.6% had abdominal pain, 54.5% had general malaise or asthenia, 54.5% had anorexia, and 36.4% had unexplained hemorrhage. Four confirmed patients died while 7 recovered with treatment which included correction of low blood volume and electrolyte balance, nutritional support, pain relief, hemostasis, antipyretic treatment and management of diarrhea. Signs of severe bleeding, for example, black stools or hemoptysis, were associated with poor prognosis.

There were three shifts for nursing personnel every day, morning shift (8AM–2PM), afternoon shift (2PM–8PM), night shift (8PM–8AM) staffed by 4, 4 and 2 nurses on duty respectively. The nurse scheduling was in accordance with the "morning–morning–afternoon–night" alternation rotation mode. Nursing administrators established the nurses' job descriptions and responsibilities. The workflow information for each shift was pasted on the office wall for ease of reference by staff.

Nurses were responsible for: replenishing materials, medications, and disposable supplies; transcribing and processing the orders, charging nursing documents and ward diary; registering new patients; and assisting personnel to wear PPEs. When nurses entered the ward they needed to take responsibility for applying nursing rounds, taking vital signs and reporting through a calling and answering system; oral medication administration, peripheral vein catheter insertion and intravenous infusion; psychological counseling or reassurance; and supervising hygienists. In view of the particular working environment of ETU, nursing managers used job memoranda before entering the ward, cycled alternately between observation and treatment wards, and established an innovative scheduling information release system to improve the care quality and guarantee patients' safety.

It is important to gain experience from ETUs set up during this epidemic in Africa, especially in Liberia, Guinea and Serra Leone where the health care system is particularly inadequate for appropriately managing and containing infectious diseases [3]. The correct level of isolation for patients with EVD in the ETU and which are the most essential medical and nursing interventions are still issues which are uncertain and under discussion [4]. A specialist committee is essential to provide a source of reference and advice for decision making in crucial procedures as there is little known of this deadly disease. There has been limited published experience from health care facilities exposed to the risks of transmission during invasive procedures and close body contact [5]. In our experience medical workers who had direct contact with blood and body fluid directly had more serious symptoms and signs than patients exposed through attendance at funeral ceremonies. There have been many personal protection protocols announced by the WHO. In our experience the Principle of "Extreme Caution" is never to be underestimated in order to reach the "Zero Infection" goal among medical and nursing staff. As an emerging infectious disease, EVD is not "horrible monsters" if medical and nursing staff strictly follow the personal protection principles.

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Adverse effects of political sanctions on the health care system in Iran

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he United States has long leveraged economic sanctions as powerful instruments to achieve foreign policy objectives [1]. Economic sanctions have been described as a "cheaper form of coercion, less aggressive than war with fewer human costs, and more politically feasible" [1]. Sanctions may be implemented as tariffs on imported goods, quotas on how much can be imported or exported, embargoes that prevent all trade between countries, or non-tariff Barriers that include other non-tariff restrictions on imported items [2]. No matter what type of sanction is used, the end goal is the same: to force a change in behavior [2]. The United States particularly favors investment withdrawals, trade embargoes and foreign aid reductions to coerce foreign countries into compliance with its foreign policy objectives. However, many question the effectiveness of economic sanctions and, while policymakers debate this, what is often understated is the hidden cost of US diplomacy: the cost to the citizens of the country in question, particularly on their health care sector. The goal of this viewpoint is to bring attention to the impact that economic sanctions can have on the health care system in the impacted nation.

IRAN

One such nation that has been crippled by economic sanctions is Iran. The political sanctions, set on Iran since 1979, have attempted to spare the average citizen from harm by specifically excluding the health care system from trade restrictions. However, the health care system is indirectly affected by the sanctions, as we have learned from personal interviews with physicians in Iran and by reading locally published articles during the summer of 2013. One effect of the economic sanctions is that the purchase of health care supplies must be done via a currency transfer that has become difficult and unreliable between Iran and the western world [3]. The *Economist* writes that "many companies and financial institutions remain reluctant to trade with Iran for fear of penalties," and that this is likely to be affecting the importing of goods, including medicine [3]. The Iranian professor and pharmacist, Cheraghali, writes [4]: "Although almost all sanctions in the recent decades had provisions for exemptions of medicines and food stuffs, sanctions (through complications in transportation, difficulty in transferring hard currencies or either lack of capital) commonly lead to disruption of health services and even basic nutrition of the ordinary people in the sanctioned countries."

Having difficulty trading with the West, the Iranian government is currently trading with its eastern allies. This exchange is indeed helpful for Iran to obtain basic supplies, however, many newer medications are still under a pharmaceutical patent and not being manufactured outside of

Economic sanctions are widely believed to be a peaceful alternative to war: sparing harm to the average citizens of a nation while putting firm pressure on their government to elicit a change. This generalization does not take into account the often overlooked impact sanctions can have on a nation's healthcare system and thus indirectly on its citizens.

the United States or Europe, limiting Iran's access to them [5]. Some supplies are being manufactured within Iran, which is a limited method of manufacturing, as the limit on currency transfer has made importing starting material such as active pharmaceutical ingredients and finished products difficult and often impossible for Iran [4]. The sociologist S. A. Hosseini writes [6] that the "quality of pharmaceuticals and treatment of patients have been affected due to changing the sources of imported medicines and raw materials for locally produced pharmaceuticals."

A pediatric surgeon from one of Iran's largest public academic hospitals expands on this when he expresses his understanding, based on personal experience, that "the sanctions were not supposed to be imposed on medicine, however, because it has become difficult to transfer money to pay for drugs, the sanctions have indirectly affected medicine. Approximately 50-60% (a personal estimate) of drugs cannot be manufactured in Iran because there is also a lack of starting materials. Suturing material, for example, is in shortage and is now either made in Iran or bought from China, both of which yield lower quality sutures (in the physicians experience)." An ENT surgeon from a private day surgery clinic adds that Iran is "coping by getting the drugs at a more expensive price from other countries, such as Dubai. Some drugs, [they] cannot even get from anywhere." These are the personal opinions of the contacts interviewed in Iran and not based on official reports.

Faced with a decreased access to medication [4,6,7], Iran's health care professionals are burdened with the unenviable task of determining where, and to whom, their resources should be allocated. While resources are typically allocated based on need, with fatal diseases and emergency surgery as the highest priority, supplies are limited even for patients with the greatest need. An ENT surgeon describes his thoughts on Iran's current situation: "Things are harder and

Iran's healthcare system has been indirectly affected by the U.S. sanctions in terms of availability and affordability of medicine, as well as their ability to contribute to the global research community.

some drugs are no longer found. Transplant and cancer patients suffer the most because of the lack of drugs. Things that are scarce are instruments, like positron emission tomography machines, and drugs, like chemotherapy and anesthesia."

Conversations with two Iranian anesthesiologists paint an even more lucid picture of the adverse effects of the medicine shortage in Iran. An adult anesthesiologist in a private practice cited remifentanyl and isoflurane as two of the more common drugs for which there was a shortage of supply. At a public academic hospital, a pediatric anesthesiologist commented on the medicine shortage and provided an example of how the shortage directly affects the Iranian children: "Sevoflurane is used to induce when a child is agitated, but it is expensive so we often use halothane instead. Halothane is an older drug and does not induce anesthesia as quick, however, it is cheaper and more available now." Aside from being outdated, halothane may lead to severe side effects, such as hepatic necrosis (which is most often unpredictable and not dose-dependent). It should be used as a drug of last resort when newer medication is unavailable.

In addition to a shortage of resources, Iran has also been isolated from the international research community. Recently, the Dutch publishers Elvesier sent a note to their network of US based editors and reviewers encouraging

> them to "avoid handling manuscripts if they include an author employed by the government of Iran" [8]. The pediatric surgeon mentioned before addresses his personal experience with this: "... academic research has been affected, as it has become harder to publish articles from Iran; the articles are less likely to be accepted into academic journals." Iranian researcher, Saeidnia, gives further insight into Iran's isolation from the global academic community when explaining that there are "many problems with money transaction in order to do scientific activities, for example [for] payment of publication fees, society subscription fees, or registration fees in



Photo: Courtesy of Roxanne L Massoumi, personal collection

international congresses" [9]. This is consistent with Cheragali's claim presented above that the health care system is being indirectly affected because of the limitations on currency transfer [4].

IRAQ

When regarding Iran's current situation, it begs the question: is Iran an isolated occurrence, or have sanctions adversely affected other countries' health care sectors with regularity and been ignored? The neighboring country of Iraq's health care system was affected by the US-led economic sanctions implemented on them from 1990–2003 [10]. Much like the situation in Iran, the economic sanctions in Iraq, which were believed to have spared its health care system, adversely affected it through the inability to transfer currency and a resulting shortage of medicine and medical instrumentation. According to the scientist Clare Sansom, "Doctors and technical staff found it almost impossible to keep even these [cobalt 60 radiotherapy] machines in service during the sanctions, because of import restrictions, difficulties with equipment manufacturers, and bureaucracy," and she describes a lengthy waiting list for treatment of tumors, even those as severe as intracranial neoplasms [11].

Iraq did not recover quickly once the sanctions had been lifted and, over a decade later, their health care sector remains unstable. Today it is considered "weak, with non– functioning equipment, inadequate drug supplies, and a fragile infrastructure" [10]. While this is a complex issue involving many factors, the instability that sanctions created in the health care system are a major contributing factor. Sansom [11] notes Iraq's position in the global medical sphere: "Iraq has been almost completely isolated from the international community for more than a decade; medical journals and even textbooks were unavailable, and there were no opportunities for doctors to travel abroad." Medicine continued its globalization throughout the 1990s, but Iraq, with its weak infrastructure, was excluded from sharing in the international community's knowledge. As a result, Iraq's health care sector continues to lag behind as those of other countries rapidly advance.

POST–SANCTION REBULDING AND THE UTILITY OF SANCTIONS

Both Iran and Iraq had health care systems that deteriorated as an indirect result of political sanctions. It is important to note the difficulty Iraq's health care system had in recovering from sanctions, as we foresee Iran traversing the same, rough road. Although the Iranian and Iraqi governments are markedly different, Iran will need to take similar steps as Iraq to rebuild their infrastructure. Iraq was ill equipped and unable to take these necessary steps, and by bringing Iraq's struggle to light, a similar fate may be avoidable for Iran.

A post-sanctioned era in Iran may be in the near future and policy-makers should begin devising a plan now that would help physicians provide better care as soon as restrictions on resources are lifted for Iran. The negative costs of sanctions on the average citizens of a country are very real and must be strongly considered prior to implementing the sanction. While they may be effective in pushing governmental policies, sanctions negatively impact common citizens and their health care, as seen in both Iran and Iraq. Cheraghali argues [4]: "There is now consensus among political scientists that the record of sanctions in achieving their stated objectives is low. Instead, ordinary people who live in sanctioned countries have to bear costs attributed to the sanction." While foreign policy objectives often leave no alternative to economic sanctions, politicians and their constituents, alike, should be cognizant of the negative effect sanctions can have on health care systems.

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Why are girls still dying unnecessarily? The need to address gender inequity in child health in the post–2015 development agenda

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The 40-year anniversary of the United Nations 'International Women's Day,' was celebrated on 8 March 2015. As we approach the end of the Millennium Development Goals (MDGs), we reflect on the gender debate that has arose amidst tackling MDG4 and highlight the need for greater gender equality in measuring child health outcomes in the post–MDG era in line with MDG 3 (see **Box 1**).

NEED TO PROFILE GENDER AS A DETERMINANT OF CHILD HEALTH INEQUITY

In recent years, several key UN reports and articles have begun to articulate the gender gap that exists in child health outcomes [1–3]. Indeed, it has been the UN which has taken a lead in promoting gender equality internationally by requiring all UN entities to mainstream gender and promote gender equality as mandated by the Beijing Platform for Action (1995) and ECOSOC resolutions 1996, 1997, 2006 and consolidated by the quadrennial comprehensive policy review 2012 (General Assembly Resolution 67/226). According to the 2012 World Development Report, gender equality is at the heart of development and "…too many girls and women are still dying in childhood and in the reproductive ages" [4]. Perhaps it is a reflection on the relative success of MDG 3 and 4 (despite it not being likely that the numerical targets will be achieved in time) that it has helped to raise the issue of gender in child health and the need for more equitable goals in the future.

Leading international organisations have developed organisation specific gender action plans, policies or guidelines in the past two decades in order to tackle gender imbalance issues in its organisational activities (see **Box 2**).

The authors congratulate recent efforts to collect gender disaggregated child health outcomes data by Inter-Agency Group for Child Mortality Estimation (IGME) and Countdown 2015 as the first step to enable the profiling of gender as a determinant of child health inequity. Nevertheless, if gender is to be mainstreamed as a determinant of child health, future country achievement profiles should require nations to highlight sex disparities in coverage of life saving interventions, especially in countries where girls are known to be subject to discrimination in health care access and outcomes. In other words, it should become the norm, rather than the exception, to report sex–differentiated data for child health indicators. In addition, reporting health interventions

There is need for better quality evidence on the role of gender in child health achievements both globally and regionally.

VIEWPOINTS

Renewed efforts are needed to ensure that gender equity is achieved in child health globally. Countries with excess female child mortality should be prioritized in these efforts.

which have been proven to reduce maternal, newborn and child mortality rates by gender would prove valuable to better realign services and make targeted policy steps.

In response to the challenge of collecting better gender data and developing an effective response, we discuss some of the challenges reported in the literature of researching gender and child health and their potential solutions. We also look briefly at the example of India; one country in which there is evidence of severe discrimination against girls in child health care outcomes, to provide a perspective of the challenge that remains ahead.

RESEARCH ISSUES AND SOLUTIONS: GENDER AND CHILD HEALTH

Data recording

There are major challenges to determine whether improvements in child survival are seen in both males and females. The UN Sex Differentials in Childhood Mortality [5] suggests that "[t]his is due to the inadequate nature of birth and death statistics in most developing countries. In the absence of complete vital registration, mortality estimates

for these countries are derived primarily from sample surveys and population censuses, through questions posed to women about the survival of their children. Such estimates can be subject to a great deal of uncertainty due to small sample sizes, as well as biases affecting the consistent reporting of all children."

The problems of data recording and collection have been further complicated by use of different surveys over different time periods and non–systematic methodologies, making comparisons challenging.

In order to address this problem, IGME was formed in 1994 to provide a uniform source of estimation for child mortality, and has produced sex—disaggregated data since the publication of UN's Sex Differentials in Childhood Mortality in 2011. This marks a significant advance towards

profiling and subsequently tackling the issue of gender inequities in child health and mortality.

However, there is a need for more and better quality evidence on the role of gender in child health achievements both globally and regionally. Identifying and incorporating indicators beyond generic health and disease outcomes by sex is crucial to understand how to modify the impact of gender based discrimination. Disaggregated data that incorporates age, region within a country, wealth and education of the family are important covariates to be studied in relation to gender when looking at child health care access and outcomes. Fostering research in gender inequality in child health is essential to allow for a more detailed analysis to characterise the precise scale and nature of the inequity and to make a substantial stab at the problem.

Biological sex differences

There is evidence in the literature to suggest that females have a biological advantage in survival over males up to age 5 years, but especially in the 1st year of life, due to being less vulnerable to congenital disease, infection, and perinatal illness including perinatal trauma, intrauterine hypoxia, birth asphyxia, prematurity, neonatal tetanus and acute respiratory distress syndrome [6]. The survival advantage for girls tends to increase as total mortality levels for a country decrease and this is postulated to be associated with distributions in the causes of death [7]. In developed countries, infectious diseases account for a lower number of causes of death and perinatal, congenital and external causes form a larger proportion of deaths between ages 1–5. Therefore, the female advantage in child mortality would increase as-



Photo: Courtesy of Indrani Kashyap, personal collection

suming that there is no health discrimination based on sex [8,9].

With these expected biological advantages taken into consideration, can we profile which countries have the worst records for gender inequity for under–five (U5) mortality?

Post-Alkema: Using estimated-expected mortality ratios

We have profiled the excess U5 mortality using the data from Alkema et al., which has updated Sawyer's model [2], to look at excess female mortality using a novel method of estimated-to-expected mortality ratios [3]. Using a Bayesian hierarchical time series approach, Alkema et al. estimate country-specific mortality sex ratios for infants and U5 children for 195 countries from 1990 to 2012. They simultaneously assess the relationship of these mortality estimates with population sex ratios to highlight the expected and the excess female mortality rates in countries with outlying sex ratios. The authors identified 15 countries with outlying U5 sex ratios, and among these, 10 had higher than expected female mortality in 2012. For the majority of these countries the excess female mortality decreased since 1990; however, the estimated-to-expected female mortality did not change substantially for most countries except in India, where they worsened. Table 1 shows the 10 countries that had higher than expected U5 female mortality; namely, Afghanistan, Bahrain, Bangladesh, China, Egypt, India, Iran, Jordan, Nepal, and Pakistan. We included in this table the ratio of estimated-to-expected female mortality rate, the number of excess female mortality for U5s and ratio of excess female deaths to total number of

Table 1. Indicators for 10 countries with higher than expected excess U5 female mortality and outlying under–five (U5) sex ratios in 2012*

Country	RATIO OF ESTIMATED— TO—EXPECTED US FEMALE MORTALITY RATE	NUMBER OF EXCESS FEMALE DEATHS	Ratio of excess U5 female deaths to total number of deaths (%)
India	1.30 (1.26–1.34)	166000 (144000–190000)	11.7
Pakistan	1.06 (1.01–1.12)	11100 (1000–21400)	2.7
China	1.08 (1.02–1.16)	8690 (2330–16100)	3.3
Bangladesh	1.06 (1.01–1.11)	3330(790–5880)	2.6
Afghanistan	1.06 (1.01–1.11)	2810 (330–5390)	2.7
Egypt	1.13 (1.11–1.16)	2250 (1860–2660)	5.6
Iran	1.13 (1.06–1.20)	1340 (590–2190)	5.2
Nepal	1.08 (1.02–1.15)	852 (227–1520)	3.5
Jordan	1.12 (1.04–1.21)	188 (63–333)	5.0
Bahrain	1.14 (1.07–1.22)	11 (6–18)	5.9

*Adapted from Alkema et al. [3]. U5 mortality is defined as the probability of dying between birth and the exact age of 5 y. Sex ratio is defined as number of males per 100 females in the population, usually normalized to 100. deaths (%). Countries are ranked in order of highest number of excess deaths (**Table 1**). India appears as the top country in terms of excess female U5 deaths.

Clearly, however, as Alkema et al. state [3], the monitoring of sex differences in U5 mortality is complicated by variability in data availability, quality (usage and often non–usage of standard errors or uncertainty intervals), changes in country specific sex differentials over time, and validation of estimates. These findings reinforce our original point for the need of better and standardised data for all countries when it comes to gender inequality analysis in child health estimates.

ISSUES IN INDIA: A BRIEF OVERVIEW

Globally, India has the largest number of child deaths and possesses significant regional variations in U5 mortality [10]. It accounts for the largest burden of excess female deaths than any other country in the world (Figure 1). The 2011 Indian census estimated that there were approximately 7.1 million fewer females than males aged 0-6 years, which was an increase from 6 million recorded in the 2001 census and 4.2 million in the 1991 census [11]. In fact, females between 1-59 months in every region in India had higher mortality compared to males [12]. Ram et al. showed significant regional variations in U5 mortality and through detailed analysis showed that the nine poorest states contained half of all people in India and just over half of all births but 71% (1 million of the 1.5 million) of deaths in children U5, highlighting the added level of regional complexity to existing gender disparities which needs to be considered for a national strategy [10].

The biggest contributor to gender imbalance in children aged 0–6 in India is likely to be prenatal sex determination with subsequent abortion of female fetuses; a practice which has increased substantially in the past 2 decades [11]. Nevertheless, there is extensive literature which also demonstrates a clear female disadvantage in health care provision and disease outcomes. For example, female children are less likely to be immunized, receive medical attention, receive appropriate antibiotic therapy or achieve good nutrition [13–15]. Therefore, to tackle gender discrimination in child health, a two-pronged approach is critical to success, addressing sex determination pre-birth and tackling discrimination in health access, preventive health and nutrition after birth.

Das Gupta et al. have argued that disparities in child health outcomes are mainly a result of a society which values its sons far over and above, and at the cost of its daughters [16]. This is a phenomenon deeply rooted in cultural, legal, social and historical reasons; hence there is a critical need for cross–disciplinary studies to help explain the gender disparities in India and guide the development of gender sensitive solutions within health care and beyond.

The government has an important role to play. Previous policies have failed to be fully effectual, and efforts to ban the sex selective abortion of females has been limited by poor implementation at the state and local level [17–19]. More recently, the Government has shifted the focus to small administrative areas through the National Rural Health Mission launched in 2005 [20] and more recently the National Urban Health Mission [21]. Ram et al. have

Box 1. Summary of Millennium Development Goals 3 and 4

Goal 3: Promote gender equality and empower women Eliminate gender disparity in primary and secondary education, preferably by 2005, and in all levels of education no later than 2015

- 3.1 Ratios of girls to boys in primary, secondary and tertiary education
- 3.2 Share of women in wage employment in the non–agricultural sector
- 3.3 Proportion of seats held by women in national parliament

Goal 4: Reduce child mortality rates

Reduce by two-thirds, between 1990 and 2015, the under-five mortality rate

- 4.1 Under-five mortality rate
- 4.2 Infant mortality rate
- 4.3 Proportion of 1 year-old children immunised against measles

estimated that at current rates of progress MDG4 will be achieved by India in 2020, by richer states in 2014, and by poorer states in 2023 [10]. Clearly, there is a still long way to go. More efforts are needed to ensure that greater gender equality is achieved in reaching these targets across all regions in India; work that incorporates better data and research, more collaboration across sectors and agencies, and strong and effectual government policies that are based on evidence.

CHALLENGES AND RECOMMENDATIONS FOR FUTURE WORK

There is a wide scope for future work into gender and child health. It is not only an important area of research, but also at present, an under–appreciated one. In particular, we have highlighted the need for progress in India, which has the largest number of excess female mortality and is home to one fifth of all children in the world (**Figure 1**).

The need for better quality data and research in child health and gender is unquestionable [22]. The global scientific community has a central role to play in the efforts to unmask, characterise, and explain the issues in a language that makes sense to governments and the international community; this is at the core of helping governments and international organisations to implement evidence based policies and programmes. Indeed, if gender is to be mainstreamed as a determinant of child health, future country achievement

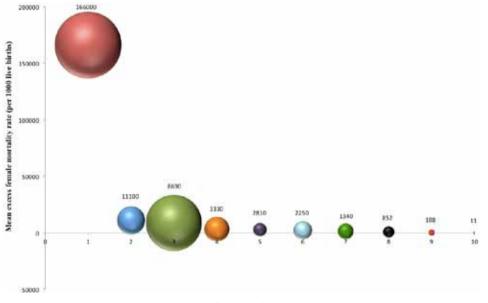


Figure 1. Ten countries with higher than expected excess under-five (U5) female mortality and outlying U5 sex ratios in 2012. Legend: 1 – India, 2 – Pakistan, 3 – China, 4 – Bangladesh, 5 – Afghanistan, 6 – Egypt, 7 – Iran, 8 – Nepal, 9 – Jordan, 10 – Bahrain. The bubble chart was created using UNICEF statistics and data from Alkema et al. [3] to demonstrate the 10 countries with outlying U5 sex ratios and higher than expected excess female U5 mortality. Countries are ranked in order of highest ratio of excess female U5 mortality to total number of U5 mortality. The size of the bubble corresponds to the total U5 population in each country, emphasizing the importance of addressing gender issues in child health in countries with large child populations. Source: UNICEF statistics, available at http://data.unicef.org/resources. VIEWPOINTS

profiles should require all nations to highlight sex disparities in mortality and coverage of life saving interventions. As the evidence in India highlights, there are two key time points in gender bias; pre–birth and post birth. More studies are needed to look at both prenatal sex determination and health access and outcomes in children.

Gender is commonly thought to be a development problem and therefore, tackling development issues such as poverty and education, could be seen as a good response to gender discrimination in child health care. However, studies in India have demonstrated that gender based discrimination against women has deep social and cultural roots and relates to family organisation norms [23,24]. There is evidence that gender bias against girls has become so deeply-rooted in some South Asian countries, and that it persists or worsens in more educated and richer families, compared to those who are poorer and less educated [25]. In the last two decades, both biomedical and social researchers have collected and analyzed evidence on different aspects of sex differentials in mortality especially in children. However, there is still a need for a more comprehensive model explaining these differentials and including the biological, social, cultural and economic factors. Further research, which incorporates the determinants of health, could help tackle discrimination against girls in different contexts [22].

Gender inequity in child health is certainly an important global health issue that requires a global solution. Address-

Box 2. Organisations identified through a Google Scholar search of 'gender' or 'sex' and 'policy' or 'guideline' or 'framework'

African Development Bank Asian Development Bank Bill and Melinda Gates Foundation Council of Europe Department for International Development (DFID) European Union Global Alliance for Vaccines and Immunisation (GAVI) Global Fund The International Federation of Red Cross and Red Crescent Societies (IFRC) Organisation for Economic Co-operation and Development (OECD) Save the Children The United Nations Children's Fund (UNICEF) World Bank World Health Organisation (WHO)

ing gender bias in child health formally in a post–2015 development agenda would give greater impetus for a more effectual and coordinated global effort to invest, address, and make progress to reduce the inequity. Indeed, when future improvements in health outcomes for children are made globally in the post–MDG era, they should be recognized for being equitable as they are now for reaching total targets.

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Tip of the iceberg: Extra–haematological consequences of early iron deficiency

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ver a third of the global population is estimated to have Iron Deficiency (ID). It manifests during all stages of life and especially during times of accelerated growth phases, mainly affecting infants, adolescents and pregnant women.

ID has been shown to be associated with poorer cognitive, motor and behavioural development, including lower intelligence quotients (IQ) in children [1]. It is also associated with poorer pregnancy outcomes for mothers and infants. This raises the question of the global effects of ID, in terms of cognitive abilities, economics and productivity. This viewpoint reviews some of the recently discovered extrahaematological effects of ID and its relevance to modernday society, in both developed and developing countries.

DEFINING IRON DEFICIENCY

Long-term negative iron balance leaves the body with no measurable iron stores, causing insufficient supplies for cel-

Iron deficiency in early pregnancy and childhood can potentially have long-lasting effects on brain development and cognitive abilities and is ultimately engrossed with many confounding factors which need to be separated from the disease process in order to appreciate the real impact of this condition lular processes. ID is at the end of a continuum (**Figure 1**), where the most severe clinical consequence is iron deficiency anaemia (IDA). The other forms of ID tend to be asymptomatic. A good indicator of ID is by diagnosis of anaemia in combination with low serum ferritin, as established by the World Health Organisation (WHO). It is estimated that ID is twice as prevalent as anaemia and that approximately half of all anaemias are due to ID. Approximately one quarter of the world's population has anaemia, with the most common cause being due to ID. In the UK, 21% of female adolescents and 18% of women aged 16–64 years are iron–deficient [3].

CONSEQUENCES OF IRON DEFICIENCY IN PREGNANCY

Pregnancy is a physiologically iron–depleting state as maternal iron stores preferentially transfer to the foetus *in utero*. Many women enter the pregnancy state with anaemia, as previous studies have shown, and many having no iron stores when becoming pregnant [4]. This suggests that they have insufficient levels required for adequate development of the foetus and placenta and for blood loss during childbirth.

Maternal haemoglobin levels have been found to have a U–shaped association with low birth weight infants [5,6]. An Indian retrospective study showed a negative correlation between serum ferritin <10 µg/L and birth weight [4]. Many interventional studies have shown increases in birth weight by a modest amount when pregnant women are given iron–repletion [7].

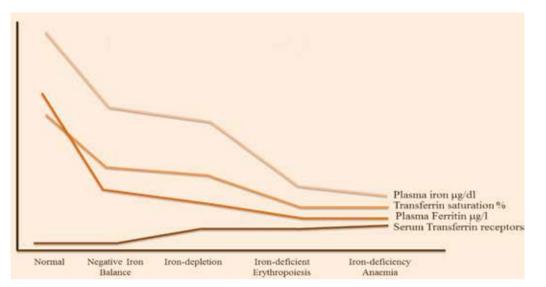


Figure 1. Serum iron changes in the stages of iron deficiency. Source of data: Clark, 2008 [2].

CONSEQUENCES OF IRON DEFICIENCY IN CHILDREN

Although rates of IDA have been steadily declining for decades, it is markedly prevalent in poor, minority and immigrant groups [8,9]. A recent study looking at specific cognitive domains of ID infants, found that they were suffering from poorer attention and memory processing (lower scores on recognition memory, object permanence and memory encoding/retrieval) [9]. Another study showed that infants with IDA had poorer high–speed information processing times, in comparison to non–anaemic infants– a predictor of future IQ [1].

Rodent models have shown that during critical brain development, a lack of iron causes defects in post-translational incorporation of iron into haemoproteins (haemoglobin and cytochromes) [8]. The lack of cytochromes in the frontal lobe and hippocampus suggests a reduction in cerebral metabolism due to low levels of ATP [8]. Iron-containing monoamines are predictably acutely affected but it is postulated to cause longer-term effects on dopamine metabolism in particular, which is known to regulate cognition and emotion [8].

Neonatal serum ferritin levels which correlate with low brain iron and neurodevelopmental abnormalities is approximately $<35 \ \mu g/L$ [10]. There is also evidence to suggest that after a critical period of ID in the brain of rats, iron–repletion thereafter will not reverse the structural deficits [8].

Interestingly in the Costa Rican study of infants aged five years [11], whose iron status' had been corrected from infancy, still scored lower on mental and motor functioning tests, consistent with other studies – even in the case of corrected haemoglobin levels (>100 g/L).

Studies assessing the effects of ID on social behaviour found that iron–deficient children were more wary, hesitant, unhappy and kept closer to their mothers [8]. In another study, infants who did not receive prophylactic iron also showed poorer social–emotional outcomes [12].

CONSEQUENCES OF IRON DEFICIENCY IN ADULTS: EFFECTS ON PRODUCTIVITY

The effects of IDA can be insidious and subtle. In an individual with ID in infancy or in early childhood, the irreversible effects on cognition and social development are likely to have an impact in later life. Consequently, the effect of ID on adult productivity, which has been shown to affect the economy in the long run, is not well recognised, and therefore significant consideration in tackling the problem is lacking [12].

Chronic undetected ID from childhood may lead to lower than expected IQs and fewer skill acquisitions in adults affecting their productivity levels. One of the most tangible outcomes of working adults is of productivity measures. It

Long-term studies are needed to assess whether normalisation of cognitive abilities with iron repletion therapy occurs, as they are currently sparse in the literature.



Photo: A Cambodian Lucky Iron Fish, which is added to cooking water to reduce iron deficiency. Photo by Dflock (Own work) [CC BY-SA 4.0], via Wikimedia Commons

can be used to objectively compare outcomes between countries. In this context, productivity can be defined as the efficiency of adults in the workplace, with Gross Domestic Product (GDP) used as the unifying unit to compare the effects on adults with ID to those with normal iron status. Although most data are mathematically derived due to variations in data collection in less developed countries, this is still important in understanding some of the long– term effects of ID.

Losses in productivity may be attributable to reduced aerobic capacity both acutely or from persisting suboptimal academic/emotional/social performance from infancy [13]. A study carried out in low--income Asia estimated productivity losses of 17% for workers in labour--intensive jobs, and 5% for moderately active jobs due to ID [12].

An economic study of ten countries assessing the impact of ID on GDP showed a loss of 2.0–7.9% [13] (estimated US\$ 9.78 billion/annum, using 2005 figures [14]). The effects of ID on an individual can be relative to the development status of the country they are living in which also has implications for the relative accountability of GDP losses in any given individual.

In a less developed country, the majority of workers are in labour–intensive jobs and the prevalence of ID is likely over 50%. ID is less likely to have an impact on GDP losses but may have a larger impact on their lives in supporting their family/community. On the other hand, in developed countries, where most working adults are in white–collar jobs and the prevalence of ID is considerably lower, they are still likely to have a larger impact on GDP.

PUBLIC HEALTH CHALLENGES

The insidious and subclinical effects of ID, regardless of when it appears in an individual's life time, are clearly problematic. The difficulty with analysing the extra-haematological consequences of ID is mainly due to the fact that there are a multitude of factors which make it very difficult to separate the true effects of chronic negative iron balance.

The evidence for the associations between maternal ID and its effect on pregnancy outcomes is based on some important studies. Anaemia in the first and second trimester of pregnancy can demonstrate warning signs of subclinical ID, putting unborn infants in a sub–optimal environment for brain development.

Consistent results highlight the suboptimal development of the hippocampus, which is a seminal region of the brain used in memory function. The most surprising and worrying finding in this area was the fact that iron–repletion at any stage after the first two years of life has minimal effect on the reversibility of neurodevelopment in the hippocampus (although it may improve in other domains) [8].

The evidence regarding the predictability of poorer memory and learning in children with early ID is concordant with most papers studying cognition in children. Some of the specific differences observed included poorer attention, memory processing and lower IQ scores [8].

There is consistency of study results showing modest improvement in function with iron–repletion therapy. With pregnant women, iron–repletion tends to increase the birth weight of the infant when compared to predicted weight, but there is still a lack of normalisation. Similarly, iron–repletion in young children tends to improve cognitive and behavioural parameters, but the differences are not normalised. One of the biggest limitations to these findings is the fact that trials have not looked at reversibility of function long–term, so it is unclear whether iron–repletion eventually causes normalisation of cognitive abilities or not.

It is well understood that the loss of aerobic capacity in IDA causes acute changes in productivity. The effects of chronic negative iron balance have been implicated in financial losses made by whole nations. The study by Horton and Ross [15] demonstrates a crude but humbling awareness of the staggering loss of economy in the working population, and it highlights some of the problems in this area in tangible terms. Although the dominating employment sectors vary from country to country, it is still an appreciable loss made globally.



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Remoteness and maternal and child health service utilization in rural Liberia: A population–based survey

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John Kraemer Department of Health Systems Administration Georgetown University 3700 Reservoir Road, NW 231 St Mary's Hall Washington, DC, 20007, USA jdk32@georgetown.edu **Background** This study seeks to understand distance from health facilities as a barrier to maternal and child health service uptake within a rural Liberian population. Better understanding the relationship between distance from health facilities and rural health care utilization is important for post–Ebola health systems reconstruction and for general rural health system planning in sub–Saharan Africa.

Methods Cluster–sample survey data collected in 2012 in a very rural southeastern Liberian population were analyzed to determine associations between quartiles of GPS–measured distance from the nearest health facility and the odds of maternal (ANC, facility–based delivery, and PNC) and child (deworming and care seeking for ARI, diarrhea, and fever) service use. We estimated associations by fitting simple and multiple logistic regression models, with standard errors adjusted for clustered data.

Findings Living in the farthest quartile was associated with lower odds of attending 1–or–more ANC checkup (AOR=0.04, P<0.001), 4–or–more ANC checkups (AOR=0.13, P<0.001), delivering in a facility (AOR=0.41, P=0.006), and postnatal care from a health care worker (AOR=0.44, P=0.009). Children living in all other quartiles had lower odds of seeking facility–based fever care (AOR for fourth quartile = 0.06, P<0.001) than those in the nearest quartile. Children in the fourth quartile were less likely to receive deworming treatment (AOR=0.16, P<0.001) and less likely (but with only marginal statistical significance) to seek ARI care from a formal HCW (AOR=0.05, P=0.05). Parents in distant quartiles more often sought ARI and diarrhea care from informal providers.

Conclusions Within a rural Liberian population, distance is associated with reduced health care uptake. As Liberia rebuilds its health system after Ebola, overcoming geographic disparities, including through further dissemination of providers and greater use of community health workers should be prioritized.

The fragility of health systems in Liberia and neighboring Guinea and Sierra Leone has significantly impeded West Africa's Ebola Fever Virus (EFV) response [1]. With health systems decimated by civil conflict and an extreme health workforce shortage [2], significant barriers to health care access exist in rural Liberia, where most therapeutic services are de-

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livered from relatively centralized health facilities [3]. These barriers are exacerbated by the EFV outbreak, which, by early December 2014, had killed 175 health care workers—a health workforce disaster that will take years to overcome [4]. Against this backdrop, the country will have to rebuild its health system, with a badly exacerbated health workforce shortage—which will likely be felt most strongly in the most rural areas, where health workers were already most scarce. Better understanding care seeking and utilization in such populations will inform the post–Ebola policy process.

Prior research has found that physical distance from health care facilities is an important determinant of health in resource–limited settings. Both quantitative [5-11] and qualitative [12-14] studies demonstrate that distance, transportation costs, travel time, and attendant opportunity costs disincentivize health care seeking and utilization for a wide range of health conditions, including maternal and child health (MCH) [15].

Relative distance is most often measured bluntly in research and policy planning surveys, largely due to complexities in measurement [16-17]. For example, both Demographic and Health Surveys (DHS) and Multiple Indicator Cluster Surveys dichotomize respondents' residences as urban or rural. This dichotomization is often translated to national policy and planning documents, which also generally divide populations as rural or urban, and develop strategies and allocate resources based on these categories [18-19]. Such gross categorization prevents more nuanced considerations of remoteness among rural populations, which are typically treated as having homogenous access to health services. It may obscure access issues faced by highly remote populations and lead to policy development that fails to address their needs [20]. More precise distance measurement would enable health officials to better understand distance's effect on health utilization and mechanisms by which it acts. This, in turn, would enable policymakers to optimize health systems to highly remote populations' particular needs [21]. As Liberia, Guinea, and Sierra Leone reformulate their health sectors after EFV, such nuance is important for building health systems that are both optimally efficient and effective.

In this study, we aim to estimate the relationship between distance and MCH care seeking and service utilization among a rural Liberian population in the period shortly before EFV's emergence. We hypothesized that distance to a health facility: 1) impedes care seeking and health service utilization in a dose–response manner, 2) particularly impedes access to services available only available at centralized health facilities, and 3) is associated with greater care seeking from the informal health sector.

METHODS

Sampling and survey design

This study analyzed cross–sectional data, originally collected in Konobo and Glio–Twarbo Districts, Liberia, for programmatic purposes to inform the design and implementation of a community health worker (CHW) program. The population sampled represented the target group for the CHW program, who reside in rural districts in southeastern Liberia with an estimated population of approximately 31 000 people and a population density of 12 people per square kilometer [22].

The survey was conducted in August–September 2012, which is during Liberia's rainy season. We selected households with a two-stage, representative cluster sampling method [23] using 2008 Liberian census data. At the first stage, 30 villages in the two districts were selected randomly with probability proportionate to the overall size of the two districts. We excluded Ziah Town, the only locale meeting Liberia's definition of an urban area (2000 or more people). We also excluded 25 villages because: 19 had less than 20 households, four could only be reached on foot, and 2 were only accessible by canoe. Together, the excluded villages comprised 15% of Konobo's rural population. At the second stage, a cluster of 20 households was selected by the following method: 1) spinning a laminated paper triangle on the ground in the village's center as determined by a map of the village's extent; 2) using a random number generator to select the first dwelling to survey in the direction indicated by the triangle; and 3) continuing to the next closest dwelling until 20 households were sampled. If no members of a household could be located, the next household was substituted.

The survey's purpose was to collect demographic, as well as maternal and child health data prior to implementation of a CHW-based maternal and child health program. We surveyed the woman in each household aged 17-and-older who had most recently completed a pregnancy. Women under 17 were excluded because they are considered minors by Liberian national health policies. The survey contained three modules: 1) basic health indicators 2) maternal health questions about the most recent pregnancy and 3) child health. Only participants who had completed a pregnancy within the last five years answered the maternal health module; however, if no woman in the household had completed a pregnancy in the last five years, the other two modules were still administered. The child health module was completed for each of the respondent's children who were under five and living in the home.

Survey questions were drawn mainly from the 2007 Liberian DHS survey [24]. It was independently translated to Liberian vernacular English by two staff members fluent in the local dialect. Because some participants were expected to speak only Konobo Krahn, a local, non–written language, the survey was administered by bilingual enumerators. All enumerators completed a four–day, pre–study classroom and field training. Following survey administration and entry into a Microsoft Access database, a study supervisor conducted data entry quality assurance by visually checking the first 100 entered surveys. Only one error per 770 fields (0.1% error rate) was identified so the remainder of the surveys were then entered. We also flagged missing and implausible values during data entry and summarization, to request further input from enumerators to clarify and/or update data. Enumerators reported that only one household refused participation.

Measures

We focused our analysis on maternal and child health care indicators. For maternal health indicators, we selected: 1) one or more antenatal checkups from a health care worker (HCW); 2) four or more antenatal checkups from a HCW; 3) delivery within a health facility attended by any provider; 4) post-natal care (PNC) from a HCW after delivery; and 5) receipt of the full maternal service cascade, defined as at least four ANC checkups, facility-based delivery, and PNC from a HCW. For child health indictors, we selected: care seeking for 1) fever, 2) acute respiratory infection (ARI), and 3) diarrhea if the child experienced those conditions within the two weeks preceding the survey and 4) lifetime receipt of anti-helminthic medication among children over age 1 year. While data were collected on vaccination, we did not include it in this analysis because of low vaccine card possession rates (28%).

Providers were categorized as formal biomedical, informal biomedical, and traditional. Formal biomedical providers were defined as registered facilities or HCWs. Informal biomedical services were those acquired from an informal drug store or mobile drug dispenser. Traditional services were defined as those provided by a traditional healer or the receipt of traditional, herbal medicines. (Provider definitions are provided in **Online Supplementary Document**, Table s1.)

For all outcomes, the primary analysis was whether care was sought from a recommended provider: one likely to have appropriate personnel, diagnostic capabilities, and treatments for that condition within this population. For all maternal health services, the recommended care source was a formal biomedical provider. Formal biomedical providers were also the recommended care source for ARI and fever because, consistent with policy, other providers were not trained to accurately diagnose these conditions [25-26]. For diarrhea, the recommended provider was either a formal or informal biomedical provider because both could be expected to carry oral rehydration salts, the recommended diarrhea treatment [27]. For two childhood illnesses, ARI and diarrhea, we also performed analyses to assess care seeking from any source (an indicator of demand for services) and to describe the sources from which care was sought (including multiple provider types) among those who sought care.

The primary predictor variable for all analyses was the road distance from the cluster to Konobo Health Center—the nearest formal health facility, which is located in the district capital, and the only health facility in the study area. Konobo Health Center was able to provide services used as outcome measures (eg, artemesinin combination therapy for fever and oral rehydration solution for diarrhea), and, aside from anti–helminthic treatment, these services generally were not otherwise available at the community level within the formal health care system. Distance was measured with handheld GPS devices (Garmin eTrex 10; Garmin Ltd) by field supervisors during travel to each cluster using recorded GPS tracks. Distance was then divided into quartiles and analyzed as a categorical variable.

We adjusted all analyses for socio–demographic characteristics. For all outcomes, these included maternal age (treated as a continuous variable after assessing appropriate fit using the Box–Tidwell test), current maternal marital status (dichotomous), refugee status (dichotomous), maternal education (categorized as "none," "primary only," or "any secondary schooling or higher"), and whether the village is accessible by four–wheel motor vehicles (vs only accessible by bicycle or motorbike). For child health outcome models, we also included child age (dichotomous dummy variables for each year) and gender. Finally, we included whether the cluster was located in a gold mining village (dichotomous), because recent gold discoveries in parts of the surveyed area created population movement with uncertain effects on health service access.

Statistical methods

Standard summary statistical methods were used to describe respondents' socio-demographic and clinical characteristics. Differences in descriptive characteristics between distance quartiles were tested using design-corrected chi-squared analysis for categorical variables, and linear regression for normally distributed, continuous variables.

To estimate associations between distance quartiles and the odds of various outcomes, we fit logistic regression models with standard errors adjusted for clustering. For each primary outcome, two models were constructed. First, we fit simple logistic regression models to estimate associations with each predictor. Next, we fit multiple logistic regression models, including all variables identified as potential confounders in prior literature, to identify independent associations with the outcomes of interest. Observations with missing data were excluded, and completeness of data are shown in **Table 1**. Distance quartile was included as set of dummy variables for the main analysis; models were rerun with quartiles as an ordinal variable to test for trends between farther distances and outcomes. After regression, we calculated and graphically depicted the adjusted probability of each outcome using average marginal effects, controlling for all other covariates in the full model at their observed levels.

As a robustness check, we fit the same multivariable models, but excluded refugees and villages with gold mining activities. These populations are the most likely to have moved into or between villages recently, introducing a risk of bias from the possibility that events occurred prior to moving into the study area. Through secondary analyses excluding these populations, the main analyses' sensitivity to this risk can be assessed.

All statistical analyses accounted for the clustered nature of the data using Taylor linearized variance estimation to adjust standard errors. For maternal health outcomes, data were treated as clustered at the village level. Child health outcomes were further clustered at the household level. We used Stata version 13.1 (StataCorp, College Station, TX) for all analyses. Data were analyzed in 2014.

Use of these data for research purposes was approved by the ethics review boards at the Liberian Institute for Biomedical Research and Partners Healthcare at Harvard.

Ta	b	le '	I. Resp	ondents	' socio-	-demog	graphi	c chara	cteristics	and	health	conditions	by	distance	quartile

Characteristic	1st quartile (n = 151 households) (n = 147 children)	2nd quartile (n = 163 households) (n = 158 children)	3rd quartile (n = 156 households) (n = 132 children)	4th quartile (n = 130 households) (n = 122 children)	Total (n = 600 households) (n = 559 children)	P
Maternal age, mean (SD)	37.4 (11.7)	33.8 (9.7)	32.5 (8.9)	32.6 (10.1)	34.1 (10.3)	< 0.001
Married mother	133/150 (88.7%)	133/163 (81.6%)	129/156 (82.7%)	112/130 (86.2%)	507/599 (84.6%)	0.19
Refugee	7/151 (4.6%)	0/163 (0.0%)	5/155 (3.2%)	44/130 (33.9%)	56/599 (9.4%)	< 0.001
Maternal education:						
none	66/151 (43.7%)	48/161 (29.8%)	48/153 (31.4%)	49/129 (38.0%)	211/594 (35.5%)	< 0.001
primary	72/151 (47.7%)	79/161 (49.1%)	76/153 (49.7%)	74/129 (57.4%)	301/594 (50.7%)	
any secondary	13/151 (8.6%)	34/161 (21.1%)	29/153 (19.0%)	6/129 (4.7%)	82/594 (13.8%)	
Child's age:						
<1 year	26/147 (17.7%)	23/158 (14.6%)	32/132 (24.2%)	25/122 (20.5%)	106/559 (19.0%)	0.15
1–5 years	121/147 (82.3%)	135/158 (85.4%)	100/132 (75.8%)	97/122 (79.5%)	453/559 (81.0%)	
Child's sex:						
female	63/147 (42.9%)	86/157 (54.8%)	58/132 (43.9%)	67/122 (54.9%)	274/558 (49.1%)	0.04
male	84/147 (57.1%)	71/157 (45.2%)	74/132 (56.1%)	55/122 (45.1%)	284/558 (50.9%)	
Pregnant in last 5 years:	108/151 (71.5%)	120/163 (73.4%)	109/156 (69.9%)	96/130 (73.9%)	433/600 (72.2%)	0.79
one or more ANC checkup	96/103 (93.2%)	99/120 (82.5%)	81/103 (78.6%)	43/96 (44.8%)	319/422 (75.6%)	< 0.001
four or more ANC checkups	60/103 (58.3%)	57/120 (47.5%)	48/105 (45.7%)	15/96 (15.6%)	180/424 (42.5%)	< 0.001
delivered at a facility*	40/88 (45.5%)	56/107 (52.3%)	62/95 (65.3%)	20/68 (29.4%)	178/358 (49.7%)	< 0.001
PNC from health worker*	33/89 (37.1%)	41/107 (38.3%)	40/97 (41.2%)	18/74 (24.3%)	132/367 (36.0%)	0.05
full maternal cascade*	26/90 (28.9%)	29/109 (26.6%)	23/99 (23.2%)	5/76 (6.6%)	83/374 (22.2%)	< 0.001
ARI symptoms:	38/144 (26.4%)	31/156 (19.9%)	48/129 (37.2%)	31/119 (26.1%)	148/548 (27.0%)	0.05
sought care	24/38 (63.2%)	23/31 (74.2%)	39/48 (81.3%)	21/31 (67.7%)	107/148 (72.3%)	0.28
–formal provider	10/24 (41.7%)	5/23 (21.7%)	2/39 (5.1%)	1/21 (4.8%)	18/107 (16.8%)	0.001
–informal biomedical provider	11/24 (45.8%)	16/23 (70.0%)	31/39 (79.5%)	18/21 (85.7%)	76/107 (71.0%)	0.008
-traditional provider	5/24 (20.8%)	3/23 (13.0%)	5/39 (12.8%)	9/21 (42.9%)	22/107 (20.6%)	0.03
Diarrhea symptoms:	47/146 (32.2%)	65/155 (41.9%)	65/130 (50.0%)	54/119 (45.4%)	231/550 (42.0%)	0.03
sought care	20/43 (46.5%)	45/62 (72.6%)	42/62 (67.7%)	26/52 (50.0%)	133/219 (60.7%)	0.01
–formal provider	8/20 (40.0%)	10/45 (22.2%)	0/42 (0.0%)	2/26 (7.7%)	20/133 (15.0%)	< 0.001
–informal biomedical provider	13/20 (65.0%)	31/45 (68.9%)	37/42 (88.1%)	18/26 (69.2%)	99/133 (74.4%)	0.12
–traditional provider	1/20 (5.0%)	7/45 (15.6%)	4/42 (9.5%)	15/26 (57.7%)	27/133 (20.3%)	<0.001
Fever symptoms:	108/146 (74.0%)	116/155 (74.8%)	101/130 (77.7%)	89/119 (74.8%)	414/550 (75.3%)	0.92
sought care from health facility	46/108 (42.6%)	28/116 (24.1%)	14/101 (13.9%)	8/89 (9.0%)	96/414 (23.2%)	<0.001
One or more lifetime dewormings†	95/114 (83.3%)	106/130 (81.5%)	78/95 (82.1%)	47/90 (52.2%)	326/429 (76.0%)	< 0.001

ANC - antenatal care, PNC - postnatal care, ARI - acute respiratory infection

*Excludes all women whose pregnancies were not carried to full term.

†Excludes children under one year of age, who are not eligible for deworming.

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RESULTS

Six hundred women completed the survey. Four hundred thirty–three (72.2%) reported a pregnancy in the previous five years. The median distance to the nearest health facility was 28.9 km (km) (range 3.5–50.2 km, **Table 1**) and the median distance to the health facility in each quartile was 10.6, 22.1, 32.3, and 46.3 km, respectively. Maternal respondents' median age was 34.1 years (interquartile range [IQR] 26–40). Only 2.8% of respondents completed secondary school, and more than one–third (35.5%) received no formal schooling. 9.4% of respondents were refugees from Cote d'Ivoire.

Among women who reported a pregnancy in the past five years, 75.6% attended the ANC at least once, but under half (42.5%) completed four or more visits (**Table 1**). Among respondents who carried a pregnancy to full–term, 49.7% delivered in a health facility and 35.6% received PNC from a HCW. Only 22.2% of respondents received the full cascade of maternal services.

The median number of children younger than five years per household was 1 (IQR 1–2). One hundred six (19%) of the children were infants, and 274 (49.1%) were female. ARI, fever, and diarrhea symptoms were reported in the past two weeks for 148 (27.0%), 414 (75.3%), and 231 (42.0%) children, respectively. Among children with ARI symptoms, families sought care for 72.3%, but only 17.1% sought care from formal medical providers (**Table 1**). Among children with diarrheal symptoms, care was sought for 60.7%, including 50.2% who sought care from a recommended provider. Among those with fever symptoms, only 23.2% sought care from a health facility. Lastly, 76.0% of children over age one year had received anti–helminthic medicine at least once. We found strong inverse relationships between distance to the nearest health facility and maternal health services uptake (Table 2, Figure 1). In both the univariable (presented in the Online Supplementary Document, Tables s2s3) and multivariable models, women in the fourth distance quartile were significantly less likely than women in the first quartile to attend the ANC at least once (AOR=0.04, *P*<0.001) or four times (AOR=0.13, *P*<0.001) and the ordinal trend across quartiles of distance to the health facility was significant for both (P < 0.001 for both). Women at farther distances were also less likely to access other services, including facility-based delivery (AOR=0.41, P=0.006 for the most distant vs nearest quartile; P=0.04for trend), PNC from a HCW (AOR=0.44, P=0.009 for the most distant quartile; P = 0.04 for trend), and complete the full maternal cascade (AOR=0.18, P < 0.001 for the most distant quartile; P = 0.001 for trend)

Distance from the nearest health facility was also associated with decreased odds of health care seeking for most child health indicators. Odds of anti-helminthic treatment were lower in the fourth distance quartile (AOR=0.16, P < 0.001; P=0.001 for trend across distance quartiles). (Table 3, Figure 2). For ARI, care seeking from a recommended provider (a health facility) was significantly lower in the third (OR=0.08, P=0.004) and fourth (OR=0.07, P=0.01)quartiles in the univariable model, marginally lower in the fourth quartile (AOR=0.05, P=0.05) in the full model, and marginally significant for trend across distance quartiles (P=0.06). For fever, the odds were lower at all quartiles compared to the closest (P < 0.001 for trend; AOR = 0.06 and P < 0.001 comparing the fourth to the first quartile). There was no significant relationship between distance and care seeking from a recommended provider (a health facility or informal biomedical provider) for diarrhea.

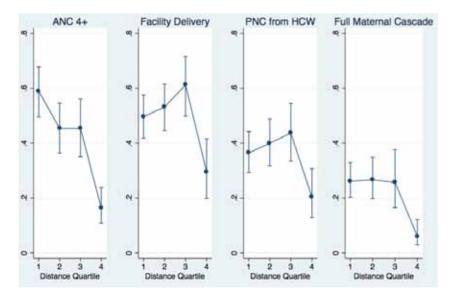


Figure 1. Adjusted probability of maternal care by distance quartile.

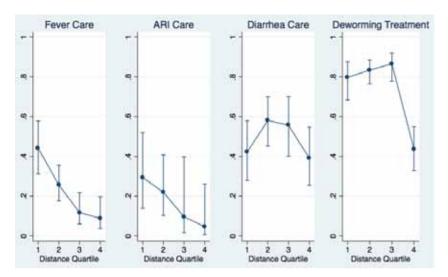


Figure 2. Adjusted probability of child health care seeking or receipt from recommended providers by distance quartile.

Table 2. Maternal health service utilization (full model)

	Antenatal clinic visit 1 +		Antenatal clinic visit	l clinic visit 4 + Facility—based delivery		PNC FROM A FORMAL HEALTH CARE WORKER		Full maternal cascade		
	Odds ratio	Р	Odds ratio	Р	Odds ratio	Р	Odds ratio	Р	Odds ratio	Р
	(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)	
Distance quartile:										
closest	Ref.	Ref.†	Ref.	Ref.†	Ref.	Ref.*	Ref.	Ref.*	Ref.	Ref. †
second	0.29 (0.13–0.67)	0.005	0.57 (0.32–1.00)	0.05	1.15 (0.72–1.84)	0.53	1.17 (0.73–1.87)	0.51	1.03 (0.62–1.70)	0.90
third	0.23 (0.08–0.66)	0.008	0.57 (0.30–1.08)	0.08	1.63 (0.89–3.00)	0.11	1.37 (0.72–2.58)	0.32	0.98 (0.47–2.06)	0.96
farthest	0.04 (0.02–0.09)	<0.001	0.13 (0.07–0.23)	<0.001	0.41 (0.22–0.76)	0.006	0.44 (0.24–0.80)	0.009	0.18 (0.08–0.40)	<0.001
Moto path	1.97 (0.99–3.91)	0.05	1.12 (0.70–1.79)	0.62	1.26 (0.74–2.15)	0.38	0.81 (0.50–1.30)	0.37	1.01 (0.61–1.67)	0.96
Gold mining village	0.67 (0.31–1.43)	0.31	0.87 (0.50–1.53)	0.63	1.26 (0.70–2.27)	0.44	0.88 (0.48–1.60)	0.66	0.62 (0.32–1.22)	0.16
Maternal age	0.98 (0.96–1.00)	0.09	1.02 (0.99–1.04)	0.16	0.98 (0.96–1.01)	0.12	1.00 (0.98–1.03)	0.86	1.00 (0.97–1.03)	0.99
Married mother	1.39 (0.73–2.64)	0.30	1.74 (0.94–3.21)	0.08	1.32 (0.75–2.33)	0.32	1.85 (1.07–3.21)	0.03	1.44 (0.76–2.71)	0.25
Refugee	2.63 (1.43-4.81)	0.003	1.15 (0.56–2.37)	0.69	1.83 (0.89–3.75)	0.10	2.07 (0.98–4.38)	0.06	1.39 (0.59–3.29)	0.44
Maternal education	on:									
none	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
primary	2.06 (1.31–3.24)	0.003	1.89 (1.26–2.86)	0.003	1.20 (0.79–1.83)	0.37	1.20 (0.78–1.85)	0.40	1.03 (0.67–1.59)	0.89
any secondary	1.53 (0.74–3.16)	0.24	2.28 (1.17-4.44)	0.02	1.85 (0.92–3.72)	0.08	1.38 (0.70–2.74)	0.34	1.36 (0.68–2.72)	0.37

PNC – postnatal care

 $*P \le 0.05$, $†P \le 0.001$, test for trend across distance quartiles.

In the robustness checks (Online Supplementary Document, Tables s4–s5), excluding populations most likely to be more highly mobile did not substantially change the relationship between distance quartiles and any health care outcome.

We also found significant relationships between distance to health care facility and choice of health care provider sought. (**Table 1**, **Figure 3**). For children with ARI symptoms, parents chose care from the formal biomedical sector less often (P=0.001) as distance increased. Care seeking from traditional providers was also more common in the fourth quartile (P=0.03). Similar patterns were observed for children with diarrhea, for which care was less often sought in the formal biomedical sector as distance increased (P < 0.001) and utilization of traditional providers increased in the fourth quartile (P < 0.001).

DISCUSSION

Greater distance from facilities is significantly associated with reduced care seeking and service utilization among the rural populations of two districts in southeastern Liberia for several high–priority maternal and child health services. Our estimates for associations between distance to health facilities and service utilization were consistent across multiple health indicators, after adjustment for preAPERS

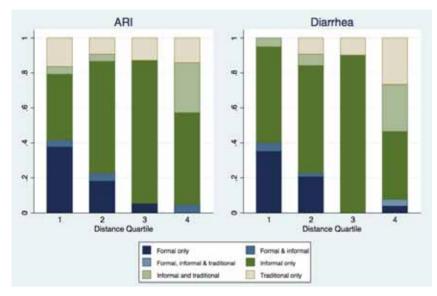


Figure 3. Care sources for ARI and diarrhea among those who sought care by distance quartile.

	Fever care seeking from	N FACILITY	ARI CARE SEEKING FROM FORMAL HCW		DIARRHEA CARE SEEKING FROM FORMAL DEWORMING TREATMENT OR INFORMAL BIOMEDICAL PROVIDER			
	Odds ratio	Р	Odds ratio	Р	Odds ratio	P Odd	ds ratio P	Odds ratio P
	(95% CI)		(95% CI)		(95% CI)	(95	% CI)	(95% CI)
Distance quartile:								
closest	Ref.	Ref.*	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.*
second	0.40 (0.18–0.89)	0.03	0.55 (0.10–3.10)	0.49	2.01 (0.86–4.71)	0.11	1.31 (0.60–2.8	5) 0.49
third	0.15 (0.05–0.43)	0.001	0.14 (0.00–5.43)	0.28	1.80 (0.64–5.10)	0.26	1.70 (0.66–4.4	0) 0.26
farthest	0.06 (0.03–0.33)	< 0.001	0.05 (0.00-1.02)	0.05	0.87 (0.35–2.17)	0.76	0.16 (0.07–0.3	8) <0.001
Moto path	0.56 (0.25–1.22)	0.14	4.35 (0.66–28.81)	0.12	1.31 (0.57–3.02)	0.51	0.47 (0.21-1.0	7) 0.07
Gold mining village	1.66 (0.69–3.98)	0.24	0.01 (0.00-0.09)	< 0.001	0.85 (0.36–1.98)	0.69	0.87 (0.41-1.8	4) 0.70
Maternal age	0.96 (0.92–1.00)	0.04	0.92 (0.75–1.12)	0.39	1.03 (0.98–1.07)	0.27	1.03 (1.00-1.0	6) 0.07
Married mother	0.27 (0.11-0.69)	0.008	0.40 (0.04–3.65)	0.41	0.92 (0.40–2.11)	0.84	1.20 (0.54–2.6	7) 0.65
Refugee	0.54 (0.21–1.37)	0.19	7.85 (0.81–76.02)	0.07	0.79 (0.26–2.41)	0.67	1.43 (0.49-4.1	4) 0.50
Maternal education:								
none	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
primary	0.50 (0.26–0.98)	0.04	0.87 (0.15–4.963)	0.87	2.62 (1.25-5.52)	0.01	1.68 (0.97–2.9	2) 0.06
any secondary	0.51 (0.19–1.37)	0.17	9.63 (1.11-83.64)	0.04	3.36 (1.14–9.88)	0.03	0.97 (0.45–2.1	1) 0.94
Child's age:								
<1 year	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.		
1–2 year	3.56 (1.45-8.74)	0.007	0.22 (0.02–2.62)	0.22	2.98 (1.29-6.93)	0.01	Ref.	Ref.
2–3 year	3.00 (1.17-7.71)	0.02	0.13 (0.02–0.99)	0.05	1.53 (0.60–3.87)	0.36	1.94 (1.01–3.7	4) 0.05
3–4 year	3.02 (1.20-7.57)	0.02	0.39 (0.07–2.13)	0.27	2.62 (1.03-6.57)	0.04	2.95 (1.43-6.0	7) 0.005
4–5 year	1.76 (0.71–4.36)	0.21	0.22 (0.03–1.47)	0.11	1.22 (0.51–2.90)	0.64	2.63 (1.32-5.2	1) 0.007
Female child	1.01 (0.60–1.68)	0.98	0.25 (0.05–1.31)	0.10	0.93 (0.51-1.70)	0.80	1.09 (0.65–1.8	1) 0.74

ARI - acute respiratory infection, HCW - health care worker

*P≤0.001, test for trend across distance quartiles

dicted confounders, and frequently of staggering magnitude. The association between distance and low utilization was particularly strong for services that, in rural Liberia, were only available at facilities or through centralized campaigns (eg, in–facility delivery and deworming). Importantly, dichotomizing this population using rural or urban categorization, as done commonly by DHS and national health ministries, would have resulted in a single homogenous "rural" risk approximation and failed to detect these large differences in health access. Because the outcomes evaluated were among the greatest public health priorities related to Millennium Development Goals, if our results represent other populations in rural Liberia and comparably remote populations elsewhere, they suggest a need to pay greater attention to remoteness both when measuring outcomes and when planning public health programs.

Our results are consistent with other findings elsewhere in Liberia. Kruk and colleagues found an association between increased travel time and lower utilization of facility–based interventions in northern Liberia [28]. Similarly, Garland et al. found transport difficulties to be a significant barrier to facility–based delivery in north–central Liberia [29]. While national DHS data also generally find care seeking and service utilization to be lower in rural than urban populations [24, 30], analyses of the effect of remoteness *within* rural settings are rarely conducted. Because our population, while very rural, is comparably remote and has similarly limited transport infrastructure to many rural Liberian settings, our findings are likely generalizable to other highly rural Liberian settings.

These findings are also broadly consistent with other data from sub–Saharan Africa. Studies in Burkina Faso [11], Ghana [31], Mozambique [32], Kenya [12], Tanzania [33], and Uganda [16] have documented an adverse association between distance and many outcomes, including service utilization, vaccination, HIV clinic absenteeism, and child mortality. In contrast, a Sierra Leonean study found no association between distance and care seeking for fever, ARI, and diarrhea [34].

With the exception of one rural Kenyan study [12], other research on the effect of distance finds weaker associations than the present study. There are several likely explanations for this. First, this population was more remote than most that have been previously studied and has, as do many highly rural areas, very poor road quality and transportation access. Measurement during the rainy season may have exacerbated these issues. However, although highly remote populations are rarely study populations, they are fairly common in many countries across the continent. Second, objectively measured distances are often dichotomized into closer and farther populations [16, 35], which obscures the effect of farther distances. Finally, many studies use self-reported distance or travel time, which frequently suffer from imprecision¹⁶ and would likely bias the measured association toward the null.

This paper's second significant finding is that farther distance is associated with greater informal and traditional provider use. For children with both diarrhea and ARI symptoms, distance did not decrease the likelihood care was sought from *any* provider, but it did markedly affect what type of provider was chosen. Interestingly, the distribution of care providers was similar for diarrhea and ARI even though the recommended providers are different. While this type of provider substitution has not been extensively studied, it is consistent with data from other West African settings [28, 34]. Use of informal health care services is particularly concerning for children with ARI symptoms because substantial evidence demonstrates that failure to accurately diagnosis and provide quality assured therapy confers poor outcomes for this condition [24]. For diarrhea, ORS and zinc are recommended treatment [27]. ORS is regularly available through informal providers, such as mobile drug dispensers and local pharmacies, and zinc often is. While formal sector care would be preferable for diarrhea, higher rates of informal sector utilization is likely less problematic for diarrhea than ARI.

There are a number of possible explanations for the substitution of services observed in this study. It may demonstrate a preference for traditional providers, or low perception of the utility of formal health care services in communities at the farthest distances, or perceptions of illness severity that correlate with distance. Alternatively, the substitution may reflect a supply problem; people may use those services that are most available in their communities. Finally, care seeking decisions may reflect costs—either for services themselves, which would not be expected to vary substantially across distances, or transportation or other transaction costs, which would likely increase with distance. This study cannot discern between these possible causes, but future research will be valuable to do so.

Limitations

First, our study population was extremely rural and poor, so the generalizability of findings in this study may be limited to similar contexts. The studied region was more rural than average for rural Liberia, but other locations in the country with similar degrees of remoteness and poor road quality are fairly common. Generalization to elsewhere in rural sub–Saharan Africa must be made with caution, but similar distances to health facilities exist in highly rural populations throughout lower population density areas on the continent. Certainly, however, our findings are unlikely to be generalizable to urban areas (with much shorter distances to health facilities and stronger transport networks) or less impoverished countries (with better access to transportation).

Second, we excluded six villages that were extremely remote, including some that were only accessible by canoe because of safety concerns accessing those villages. We did not believe the inclusion of those data justified risks to enumerators. Because these villages were particularly remote, we would expect that their health care access was worse than in villages we sampled. If this is true, the exclusions would result in an underestimate of reduced care seeking and utilization in the farthest quartile. While this introduces bias, the expected direction is toward the null hypothesis, which does not imperil our main findings. Third, some survey respondents only spoke Konobo Krhan, which is a non–written language, so enumerators translated questions directly during interviews. The use of a non–written survey can introduce challenges to data quality. We mitigated misinterpretation of questions and responses with bilingual enumerators and pre–study translation training. A similar approach is used for DHS surveys in some settings [36], though future research should explore methods to validate field translation. An alternative approach would have been to exclude participants who spoke only Krahn, which may have introduced selection bias because of socioeconomic differences between local groups.

Fourth, this data are susceptible to standard limitation of cross–sectional surveys. The causality of the associations we identified cannot be directly proved, and are susceptible to unmeasured and residual confounding. We also might misclassify distance to clinic if respondents changed residence between the date of health service delivery and the date of the survey. This misclassification should be minimal for child services, due to the short recall period, but may be more problematic for maternal services. We assessed for this risk in sub–analyses in which we excluded populations most likely to have recently moved: refugees (some of whom may have immigrated during the 2010–2011 Ivorian post–election turmoil) and residents of villages with gold mining operations. We found no substantial differences in our estimates with these populations excluded.

Finally, this study did not include direct measures of income or wealth, which some might consider a limitation because there is often a correlation between ruralness and poverty. They were not included for both technical and theoretical reasons. Income is very difficult to measure accurately in the study setting because almost all of the population are subsistence farmers and receive no cash income. Household wealth, on the other hand, is often measured in similar settings by durable good indices. However, measuring relative wealth in settings that are both very rural and very poor is challenged by a lack of supply for many goods in local villages and limited utility for others-such as mobile telephones, which cannot receive service in most of the study area. Finally, the surveyed population is universally impoverished as an absolute measure, limiting the value of relative wealth measurement.

However, by not including measures of income, we are unable to address interactions between geographic and economic barriers to care. Prior research has identified a range of other barriers to care among rural populations in sub– Saharan Africa, including poverty, socio–cultural factors, and poor quality of health services, many of which are often correlated with distance [37-39]. While examining these interactions was beyond the scope of this study, it is an important area for further study, particularly because policy interventions in this or similar settings will have to optimize interventions to simultaneously overcome multiple barriers to care for the same populations.

Policy implications

This research has several policy implications for highly rural, low-income settings. Our data demonstrate an important need to measure and report distance to health facilities precisely. Doing so will help identify the most vulnerable populations in such settings, enable more disaggregated health indicators, and augment health policy prioritization. International human rights law [40] and ethical norms [41] oblige health ministries and their development partners to promote equal access to essential health services. Our results suggest that, in order to understand and reduce geographic disparities, countries should collect granular data on distance from health services. Important progress has been made on this front. For example, DHS has begun to do so for most of their survey clusters.

More specifically for Liberia as it rebuilds its health system after EVF, this study suggests that there is a need for nuanced approaches to addressing geographic barriers to health care utilization. Ebola has decimated the health workforce—exacerbating an already dire health workforce shortage—with long–lasting consequences for facility–based care provision. Liberia is currently designing a new health workforce strategy and will likely have to increase its reliance on non–facility–based providers in remote areas.

A number of strategies may be useful in this context, including task—shifting [42]; CHW—based service delivery [43-46]; training, formalization, or partnership with traditional or informal providers [47]; mobile clinics and clinical outreach [48-49]; or cash and other reimbursements for health care seeking and/or transportation costs [50-51]. Enhancing the scope and scale of the country's existing volunteer CHW network—and increased integration between CHWs and facility—based care may be a high—yield, feasible, and sustainable option as the country builds back its health system from Ebola.

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Association between HRP–2/pLDH rapid diagnostic test band positivity and malaria– related anemia at a peripheral health facility in Western Uganda

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The detection of severe malaria in resource-constrained settings is often difficult because of requirements for laboratory infrastructure and/or clinical expertise. The aim of this study, therefore, was to explore the utility of a multiple antigen (HRP-2/pLDH) rapid diagnostic test (RTD) as a low-cost, surrogate marker of patients at high risk for complications of severe malaria. We reviewed programmatic data at a peripheral health center in Western Uganda. Available demographic and clinical data on all individuals presenting to the center who underwent an RDT for suspected malaria infection were reviewed. We fit logistic regression models to identify correlates of two outcomes of interest: 1) severe malaria-related anemia, defined here as hemoglobin ≤7g/dL and 2) receipt of parenteral quinine. 1509 patients underwent malaria testing with an SD FK60 RDT during the observation period. A total of 637 (42%) RDTs were positive for at least one species of malaria, of which 326 (51%) exhibited a single HRP-2 band and 307 (48%) exhibited both HRP-2 and pLDH bands, while 4 exhibited only a single pLDH band. There was a trend towards more severe anemia in patients with a HRP-2/pLDH positive RDT compared to a HRP-2 only RDT ($\beta = -0.99$ g/dl, 95% CI -1.99 to 0.02, P = 0.055). A HRP-2/pLDH positive RDT was associated with an increased risk of severe malaria-related anemia compared to a negative RDT (adjusted odds ratio (AOR) 18.8, 95% CI 4.32 to 82.0, *P*<0.001) and to a HRP–2 only RDT (AOR 2.46, 95% CI 0.75 to 8.04, P=0.14). There was no significant association between RDT result and the administration of parenteral quinine. These results offer preliminary evidence that specific patterns of antigen positivity on RDTs could be utilized to identify patients at an increased risk for complications of severe malaria.

Each year millions of African children are infected with *P. falciparum* malaria, and approximately 550 000 die from manifestations of severe disease [1]. In areas of high transmission intensity, severe anemia is the most common complication of severe malaria, which primarily affects infants and young children [2]. While delays in the diagnosis and treatment of malaria are associated with poor outcomes [3-5], effective management requires well–equipped hospitals with highly trained clinicians, which are lacking in many malaria endemic settings [6,7]. Mortality among children with severe malaria anemia who receive care at hospitals and referral centers has been reported as high as 10–20% [8-11], and it may be even higher among those presenting to peripheral health facilities, where human resources and acute care services, including access to mechanical ventilation, hemodialysis, and blood transfusion, are limited [12,13].

A major challenge to the identification of severe malaria stems from the rigorous laboratory–based diagnostic criteria [2,14,15]. Hemoglobin, glucose, creatinine, and lactate levels are rarely available at peripheral health facilities in resource–constrained settings [14,15]. Even light microscopy is often inaccessible because of the requisite infrastructure and technical expertise [7,13,16,17]. Without proper diagnostic tools, health care workers may misidentify and inappropriately triage cases of severe malaria [7]. An ideal diagnostic test would enable health care workers, especially nurses, midwives, and community health workers, to accurately and quickly identify patients either with or at risk for complications of severe malaria and initiate expedited management practices.

Rapid diagnostic tests (RDTs) are low-cost, simple tools for the diagnosis of malaria and are particularly valuable in settings where microscopy is not readily available [18-21]. Newer generation RDTs that incorporate multiple antigens on a single membrane have been developed to differentiate between various Plasmodium species infections. Additionally, these RDTs have shown some ability to provide a quantitative estimate of parasite density due to the differing sensitivities of the respective antigens [22-24]. Because parasite density can be a correlate of disease severity, the use of multiple antigens on a single membrane has the potential to aid in detection of severe malaria. No study, however, has examined the association of RDT band positivity with clinical parameters. Thus, we reviewed data from a peripheral health center in rural Uganda to assess for a correlation between band RDT positivity and markers of disease severity. Our overarching goal was to explore the potential use of a multiple-antigen RDT as a low-cost, scalable marker of patients at risk of severe malaria-related anemia.

METHODS

Study site

We evaluated programmatic data during the period January–March 2013, collected from the Bugoye Level III Health Center (BHC), in the Kasese District of Western Uganda (0° 18' North, 30° 5' East). The health center functions as a referral center for the Bugoye sub–county, and serves a rural population of approximately 50 000 residents. The center houses a small laboratory with staff

trained to perform light microscopy and RDTs, as well other basic tests, such as hemoglobin estimation.

Study overview

The objective of this retrospective, observational pilot study was to assess the diagnostic utility of a three–band (HRP–2/ pLDH) RDT at a resource–limited, rural health center in malaria–endemic Western Uganda.

Study procedures

We reviewed data on all individuals with fever who underwent an RDT for suspected malaria infection. We abstracted data on patient age, sex, village of residence, patient disposition, laboratory results, and medication prescriptions from clinic registers.

Laboratory procedures

Laboratory diagnosis of malaria was made using the Standard Diagnostics FK60 Malaria Ag *P. falciparum*/Pan RDT (Standard Diagnostics, Hagal–Dong, Korea). The RDT is a validated antigen detection test with three individual bands signifying the control, the HRP–2, and the pLDH antigens [23,25,26]. The presence of a control band in the absence of either a HRP–2 or pLDH result indicates a negative test. The presence of a single HRP–2 line denotes infection with *P. falciparum*, whereas a unique pLDH line indicates infection with one or more of the other *Plasmodium* species. The presence of a positive HRP–2 line together with a pLDH line indicates an infection with either *P. falciparum* or a mixed–species infection.

RDTs (Lot #090192) for the study were obtained from Kampala Pharmaceutical Industries (Kampala, Uganda), and stored in their original packaging at room temperature. RDTs were performed and interpreted by two members of the BHC laboratory staff in accordance with the manufacturer's instructions. In cases in which the control line did not appear, the result was considered invalid and the test was repeated. Faint HRP–2 and pLDH test lines were considered positive.

When available, we reviewed matched thick and thin smears for specimens with three–band positive tests. Smears were prepared using a modified Field's Stain and examined by light microscopy [27]. Asexual parasitemia of any level was reported as a positive smear. Blood smears were transported to the Epicentre Mbarara Research Center for confirmatory review, where two expert microscopists, who were blinded to the field results, independently read the slides. Hemoglobin (Hb) levels were estimated using Sahli's method [28] as is the standard of care at BHC.

Statistical analysis

Data were entered into Microsoft Excel (Redmond, WA) and analyzed with Stata 12.1 (College Station, TX, USA).

We summarized patient characteristics and compared those with two– and three–band positive RDTs using Pearson chi–squared testing. We fit univariable logistic regression models to identify correlates for two outcomes of interest: 1) severe anemia, defined as a hemoglobin <7 g/deciliter (g/dL) and 2) receipt of parenteral quinine. While the WHO traditionally defines severe malaria-related anemia a normocytic anemia of Hb <5 g/dL in children and <7 g/dL in adults, we used hemoglobin values of <7 g/dL as the clinically relevant outcome as it represents the transfusion threshold for severe malaria in adults and approaches the threshold at which transfusion should be considered in children when present with other clinical features [2,29].

Our primary explanatory variable of interest was RDT test result, defined as HRP–2 vs HRP–2/pLDH positive. Secondary explanatory variables included sex, age, village distance from the health center, village elevation, and transmission season, defined as high (January) or low (February, March). We fit multivariable models including all variables that were significant in univariable models with a pre–specified *P*–value of <0.25 [30]. A resulting *P*–value of <0.05 was considered statistically significant in the final models.

Ethics statement

Ethical approval for study procedures and data collection was provided by the institutional review boards of Partners Healthcare and the Mbarara University of Science and Technology. Informed consent was not required by the ethical review committees due to the programmatic nature of the project.

RESULTS

During the observation period, 1509 patients underwent malaria testing with an RDT. A total of 637 RDTs (42%) were positive for malaria. Of the positive RDTs, 326 (51.2%) exhibited a single HRP–2 band, 307 RDTs (48.2%) exhibited both HRP–2 and pLDH bands, while only 4 RDTs (0.6%) exhibited a single pLDH band. Characteristics of the study sample, stratified by RDT result, are summarized in **Table 1**.

Notably, the prevalence rate of HRP–2/pLDH positive results was twice as high among patients <15 years compared to those ≥15 years. The absolute number and proportion of HRP–2/pLDH positive RDTs declined during the transition from high to low transmission seasons, while that of HRP–2 only positive RDTs remained relatively stable.

Of the 307 patients with HRP–2/pLDH positive RDTs, 90 (29.3%) had corresponding blood smears available for interpretation. The majority (83/90, 92.2%) of smears from patients with HRP–2/pLDH positive RDT results demonstrated *P. falciparum* mono–infections, although there were

 Table 1. Univariable comparison of patients with positive RDT by antigen category

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CHARACTERISTIC	HRP-2 positive	HRP-2/PLDH POSITIVE	P —value
Number (n, %)	326 (51.5)	307 (48.5)	-
Sex (Male/Female)	124/202	123/184	0.60
Age (median, interquartile range):	31 (15, 58)	25 (12, 58)	0.22
<5 years (n, %)	87 (26.7)	87 (28.3)	0.64
<15 years (n, %)	192 (58.9)	216 (70.4)	0.003
Village (n, %):			
distant from Clinic	22 (6.8)	18 (5.9)	0.69
low elevation	152 (46.6)	141 45.9)	0.03
Transmission season:			
high (n, %)	119 (36.5)	164 (53.4)	< 0.001
low (n, %)	207 (63.5)	143 (46.6)	

4 mixed–species infections (2 *Pf/Pv*, 1 *Pf/Po*, 1 *Pf/Pm*). In addition, there were two non–*P. falciparum* mono–infections (1 *Po*, 1 *Pm*), which may have represented sub–patent *P. falciparum* co–infection not seen on microscopy. All four of the pLDH–only positive RDTs were identified as *P. ovale* mono–infections. Parasite density was reported for 89 of 90 of the three–band positive individuals. The mean density was 73 105 parasites/µL with a median density of 40 200 parasites/µL (IQR=12 100–103 238). Parasite densities were only available for three patients with HRP–2 positive RDTs.

The sensitivity for *P. falciparum* infections (including mixed–species infections) was 99.1% (95% CI 94.5% to 99.9%). The specificity was 75% (95% CI 53.0% to 89.4%), although only a small number of smears were prepared in patients with paired HRP–2 positive (n = 19) and negative (n = 19) RDTs. If, however, we assume that the two RDTs that were three–band positive but negative on microscopy represented true *P. falciparum* infections, as seen when confirmed by PCR in other studies [31,32], the specificity improves to 81.8%.

During the observation period, a total of 85 paired hemoglobin (Hb) levels were assessed in patients also undergoing an SD FK60 RDT. Children <5 years of age were more likely to have a Hb performed and had a higher proportion of values <7 g/dL (56.4% vs 26.1%) compared to those individuals \geq 5 years of age. The mean Hb was 7.3g/dL (95% CI 6.6 to 8.1) in patients with a HRP–2 only positive RDT, and 6.3g/dL (95% CI 5.6 to 7.1) in patients with a three– band positive RDT (β =-0.99 g/dl, 95% CI -1.99 to 0.02, P=0.055, **Figure 1**).

In multivariate logistic regression models, a HRP–2/pLDH positive RDT was the strongest predictor of severe anemia (**Table 2**). The odds of severe malaria anemia were more than double in those patients with a HRP–2/pLDH positive RDT compared to those with an HRP–2 only positive RDT (AOR 2.46, 95% CI 0.75 to 8.04, P=0.14) with a trend toward statistical significance.

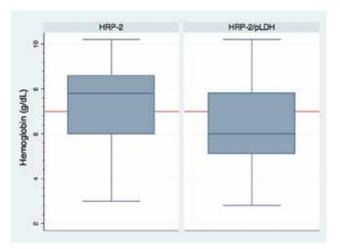


Figure 1. Box plot showing distribution of hemoglobin level in HRP–2 vs HRP–2/pLDH positive rapid diagnostic tests.

We identified 179 patients who were admitted to the inpatient ward with an admission diagnosis of malaria. RDT results were available for 116 (64.8%) of these patients. There were no differences in rates of inpatient admission between those with HRP–2 only and HRP–2/pLDH positive RDTs. Patients with HRP–2/pLDH positive results were more likely to receive treatment with parenteral quinine and anti–pyretics. In the multivariate analysis for correlates of receipt of parenteral quinine, the strongest associations were seen with three–band positive RDT and infection during high transmission season, although neither of these reached statistical significance (**Table 3**).

DISCUSSION

Our results show a trend towards patients with HRP–2/ pLDH positive RDTs having more severe malaria–related anemia that those patients with an HRP–2 only positive RDT. While previous work with the SD FK60 in a reference laboratory found a correlation between parasite density and the presence of the pLDH band [23], our findings linking three–band positivity to anemia are novel. Our findings provide preliminary evidence that multiple band RDTs, with antigens of differing sensitivity, may have the potential to serve as an adjunctive tool for the identification of patients at high risk of severe malaria–related anemia. Further studies are needed to determine if incorporating three– band positivity into malaria case management algorithms at peripheral health facilities might accurately identify patients either with or at risk for complications of severe malaria.

We postulate that the positive pLDH band, which is less sensitive than HRP–2, is a marker of higher parasite density [33-35]. Findings from our study that would support this association include: 1) nearly a quarter of three–band positive smears demonstrated parasite densities >100 000/ µl; 2) a higher prevalence of three–band positive RDTs among individuals <15 years of age who have not yet acquired protective immunity [36-39]; 3) high relative rates of three–band positive disease during the traditional high transmission season; and 4) the higher degree of anemia among patients with a HRP–2/pLDH positive RDT. We note that previous studies have shown that the degree of anemia correlated with both parasitemia and schizontemia [40].

An alternate explanation for the relationship could be HRP–2 antibody persistence leading to false–positive HRP–

Table 3. Logistic regression models for correlates of parenteral quinine

	Univar	NABLE MODEL		Multivariate model			
Characteristic	OR	95% CI	P-value	AOR	95% CI	P-value	
Male sex	1.47	0.43–4.98	0.54	_	-	-	
Age <15 years	0.89	0.25–3.19	0.85	_	-	_	
Comorbidity	3.44	0.81-2.43	0.35	_	-	_	
Antibiotics	0.63	0.18-2.26	0.48	_	-	_	
High season	6.52	0.80–52.9	0.079	5.59	0.68–46.0	0.11	
3-band RDT	2.36	0.66-8.43	0.19	1.92	0.52-7.06	0.33	

OR – odds ratio, CI – confidence interval, AOR – adjusted odds ratio, RDT – rapid diagnostic test, HRP–2 – histidine rich protein–2, pLDH – pan–lactate dehydrogenase.

*Explanatory variables with a P-value of <0.25 in the univariable model were included in the multivariable model.

	Univariable model			Multivariate m	ODEL	
Characteristic	OR	95% CI	P-value	AOR	95% CI	P-value
Male sex	1.51	0.62-3.72	0.37	_	-	_
Age <15 years	4.47	1.49-13.38	0.007	4.55	1.32-15.6	0.016
High season	0.85	0.35-2.05	0.72	_	-	_
RDT result:						
negative	Reference			Reference		
HRP–2 only	7.69	1.81-32.6	0.006	7.49	1.70-33.1	0.008
HRP–2/pLDH	18.0	4.37-74.2	< 0.001	18.8	4.32-82.0	< 0.001

OR – odds ratio, CI – confidence interval, AOR – adjusted odds ratio, RDT – rapid diagnostic test, HRP-2 – histidine rich protein–2, pLDH – pan–lactate dehydrogenase.

*Explanatory variables with a P-value of <0.25 in the univariable model were included in the multivariable model.

2 positive RDTs. Prior studies in Uganda have reported HRP–2 band specificities as low as 62% [31]. These false– positive HRP–2 tests could result after recent treatment with antimalarials, making those patients with acute illness as indicated by HRP–2/pLDH band positivity appear relatively ill.

However, our clinical experience in Bugoye suggests that very few patients seek treatment for malaria outside of the government health center, given difficult terrain and high costs associated with private facilities. In settings where there is a low probability of prior treatment, such as our site, the specificity of the HRP–2 antigen is typically higher than that associated with studies conducted at urban referral centers [31,41,42]. As evidence of this, studies from more rural sites in Uganda that have utilized polymerase chain reaction (PCR) to investigate discordant RDT and microscopy results have found the PCR–corrected specificity to be significantly higher [32,43]. Additionally, validation studies with the SD FK 60 in field conditions from other regions have reported a specificity for *P. falciparum* malaria exceeding 95% [26].

Our study, which was hypothesis generating in nature and primarily involved a retrospective review of routinely collected data, has a number of limitations. Foremost among these is the lack of available paired slides for all specimens. The available slides and Hb results were prepared in a non– random manner at the direction of the supervising clinical officer. We did, however, review smears for nearly 30% of those patients with three–band positive RDTs and Hb values for nearly 15% of patients with positive RDTs. The second major limitation of our study was that the use of the Sahlis method for Hb estimation, which while simple and inexpensive, can be prone to dilution and reading errors. We believe there should be minimal bias stemming from this method because errors would be stochastic and a single staff member interpreted all results. Finally, we performed this study at a single site and with a relatively small sample size, which reinforces the need for corroboration of these findings in larger, and more diverse patient populations. A follow up, prospective study is now under way.

CONCLUSIONS

In summary, our findings suggest that patients with HRP– 2/pLDH positive RDTs have more severe malaria–related anemia than patients with HRP–2 only positive RDTs. We postulate that the positive pLDH band, which is less sensitive than HRP–2, is a marker of higher parasite density and correspondingly, more severe anemia. These results offer preliminary evidence that multiple antigen RDTs could be utilized to identify patients at an increased risk for complications of severe malaria. If confirmed, multiple antigen RDTs may play a role in case management algorithms at peripheral health facilities. Further studies with more comprehensive data collection methods, larger sample sizes, and longer timeframes should be pursued before this approach is adopted.

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Effect of health system reforms in Turkey on user satisfaction

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Prof. Rifat Atun Harvard T.H. Chan School of Public Health Harvard University Boston MA 02115, USA ratun@hsph.harvard.edu In 2003, the Turkish government introduced major health system changes, the Health Transformation Programme (HTP), to achieve universal health coverage (UHC). The HTP leveraged changes in all parts of the health system, organization, financing, resource management and service delivery, with a new family medicine model introducing primary care at the heart of the system. This article examines the effect of these health system changes on user satisfaction, a key goal of a responsive health system. Utilizing the results of a nationally representative yearly survey introduced at the baseline of the health system transformation, multivariate logistic regression analysis is used to examine the yearly effect on satisfaction with health services. During the 9-year period analyzed (2004-2012), there was a nearly 20% rise in reported health service use, coinciding with increased access, measured by insurance coverage. Controlling for factors known to contribute to user satisfaction in the literature, there is a significant (P < 0.001) increase in user satisfaction with health services in almost every year (bar 2006) from the baseline measure, with the odds of being satisfied with health services in 2012, 2.56 (95% confidence interval (CI) 2.01-3.24) times that in 2004, having peaked at 3.58 (95% CI 2.82–4.55) times the baseline odds in 2011. Additionally, those who used public primary care services were slightly, but significantly (P < 0.05) more satisfied than those who used any other services, and increasingly patients are choosing primary care services rather than secondary care services as the provider of first contact. A number of quality indicators can probably help account for the increased satisfaction with public primary care services, and the increase in seeking first-contact with these providers. The implementation of primary care focused UHC as part of the HTP has improved user satisfaction in Turkey.

Starting in 2003, the Turkish government introduced major health system reforms to achieve universal health coverage (UHC) [1], the Health Transformation Programme (HTP), led by the Ministry of Health (MoH) with collaboration of international agencies such as the World Health Organization (WHO) [2].

The HTP brought changes to organization, financing, resource management and service delivery in the Turkish health system to address large inequities in health insurance coverage. In 2003, only 66.3% of the population was covered by health insurance. However, just 12% of the poorest expenditure decile benefited from the Green Card scheme (a noncontributory health financing scheme for the poor, separate from the health insurance schemes, financed by the Ministry of Finance and operated by the Ministry of Health, covering until 2004 cost of hospital inpatient care, but not outpatients or medicines) [1], which in 2003 covered 2.5 million people [3].

The population which lacked health insurance experienced high out–of–pocket expenditures, had variable access to health services and experienced poor health outcomes [1]. However, absolute shortage and inequitable distribution of physical infrastructure and health human resources meant that even for the insured, access to health services proved challenging. Furthermore, the dual practice of doctors in teaching hospitals (where doctors practiced both in the private and public sectors) substantially reduced the availability of public services for the insured, with many patients diverted to private practice. In particular, for financing, the health system reforms included the extension of health insurance to almost 11 million persons funded from government budget.

The health system reforms of financing were aimed at consolidating into a general health insurance organization and aligning the five parallel social health insurance schemes, namely: the Social Insurance Organization (SIO) (covering active and retired workers from the formal sector); Government Employees Retirement Fund (covering retired civil servants); Bağ-Kur (covering the self-employed and artisans); the Active Civil Servants Insurance Fund (covering civil servants in work and their dependents); and, the Green Card scheme (for poor households with incomes below the national minimum). Each of these schemes had different benefit packages and disparate contractual arrangements with provider organizations, leading to significant inefficiency and inequity within the health system. In addition, there existed a small but growing private sector with its own system of private insurers and health care providers [1].

Major changes in service delivery included the introduction and expansion of a new Family Medicine (FM) model, aimed at transforming countrywide the delivery of Primary Health Care (PHC) services, especially in rural areas. Introduction of provider choice in 2004 enabled patients to switch health service providers [4]. **Box 1** shows a time– line of the key financing and service delivery changes relating to patient experience.

Collectively, these changes, amongst others, enabled the development of a unified health insurance system and to expand health care access to establish UHC by 2011 [1,6]. The health system reforms were designed to improve the user experience of the health system, which in 2003 was

the lowest among the five major public services (health services, security, pensions, social security, and judiciary) – only 30% of the population were satisfied with the health service, where the satisfaction for the other services ranged from 50-75% [1].

User satisfaction is one of the key goals of a health system, as recognized in health system frameworks [1,7]. For the purpose of this study, satisfaction is defined as "the feeling arising from meeting the needs and desires" of the individual: a definition is taken from the Life Satisfaction Survey (LSS) in Turkey which provides the data analyzed in this paper [8]. Clearly evident in the definition is the subjectivity of the concept of "satisfaction". Being a subjective concept, a large number of factors are found to influence satisfaction at the individual level. Health system design, how care is delivered and individual characteristics influence user satisfaction with health services [9]. **Table 1** shows a summary of these factors identified in the literature.

Box 1. Timeline of Health Transformation Programme implementation

2003: Ambulance services made free; Patients no longer permitted to be held in hospitals for non–payment of fees [5]. **2004:** Green Card insurance (social security scheme for the most disadvantaged) holders covered for outpatient care and pharmaceuticals [1,5]; Conditional cash transfers introduced for pregnant women and children from most deprived households (covering 6% of population) to encourage use of services [1]; Major changes in pharmaceutical policy leads to reduction in price of drugs [1]; Patient's Right to choose a physician implemented in Ministry of Health hospitals [5]; electronic system for complaints and suggestions introduced; and Patient choice of health care provider (secondary/primary care; public and private) introduced [1].

2005: New family medicine model introduced in Düzce province [5].

2006: Family medicine introduced in Adıyaman, Denizli, Edirne, Eskişehir, and Gümüşhane provinces [5].

2007: Free at delivery primary care introduced for all, regardless of insurance status; Family medicine model introduced in Elazığ, Isparta, Izmir and Samsun provinces [5].

2008: Free emergency and intensive care services to be provided for everyone at private as well as public hospitals [1]; Air ambulance introduced, free–of–charge to entire population [1]; Cost–sharing for complex conditions in private hospitals scrapped [1].

2009: Mobile pharmacy introduced to rural regions [1]; Hospital appointment system centralised [1]; Shared payment for outpatient physician and dental services introduced [5]; Family medicine introduced to five provinces (Bursa, Rize, Trabzon, Tunceli and Uşak) [5].

2010: Family medicine model implemented nationwide [1,5].

Table 1. Summary of individual and systematic factors influencing user satisfaction with health services

Individual characteristics	System characteristics
Age: Older people are generally more satisfied [10-15] Gender: Some studies showing females are generally more satisfied, [11,16] although some showing more inconsistent results with the direc- tion of effect [10,12,13,15] Education level: less educated are found to be more satisfied in some	 Physician level: patient–centeredness and professional skills positively affect satisfaction [10,11,14,15,17,18,20,21,23-26] Visible facilities: more visibly pleasing, clean etc. facilities associated with increased satisfaction [24] Accessibility: Cost, availability, convenience of care, and waiting time
studies [16,17], inconsistent direction in others [12,13] Geographical variation: rural areas tend to be more satisfied than urban population [10] Health status: people in a good state of health tend to be more satisfied, [13,14] but findings are somewhat inconsistent [10,17-19] Frequency of visits to doctor: increased frequency, increase in satisfac- tion [20] Psycho–social determinants: various determinants associated, [10,21]	all have effects on satisfaction [10,12,16,23,24,27] Choice of provider: less choice associated with less satisfaction [16,23 Continuity of care: more continuous care increases satisfaction [10,18,27] Completeness of care: more complete care offered by physicians in creases satisfaction [27] Service delivery: more efficient processes, organized procedures, and quality of services increase satisfaction [19,26-28]
most importantly seems to be 'prior expectations of the patient' [22]. Lower expectations, higher satisfaction [19] Outcome satisfaction : increased satisfaction with better health outcomes [10,14,19,21] Socioeconomic status : inconsistent direction depending on variable used [18] Ethnicity : little consistency [12,13]	

To date few studies have analyzed user satisfaction with a nationally representative sample through a period of health system reforms (Table 1). This study uses a nationally representative annual population with a baseline at the start of the health reforms in Turkey. The data for nine consecutive years (2004–2012) of a nationally representative population surveys undertaken annually, coinciding with the time-period of the introduction of major health system reforms in Turkey, and uses satisfaction with other public services as comparators to health services, all unique in the breadth of current literature relating to user satisfaction. In this study we adjust for individual characteristics (personal, demographic and socio-economic characteristics of the respondents) to show the effects related to key system characteristics, which have changed with the rollout of HTP, have had on user satisfaction with health services in Turkey.

METHODS

Data and variables

The LSS in Turkey was implemented in 2003 as part of the Urgent Action Plan of the new Government. This plan included a duty to measure the satisfaction and expectations of citizens in all areas of the country. The LSS was first carried out as part of the Household Budget Survey, but from 2004 onwards was carried out separately on an annual basis [8], with questions fairly consistent and comparable across the years [29]. These questions are based on previous surveys and are a validated instrument for measuring satisfaction [30].

The LSS uses a two-stage stratified cluster (with household as the cluster unit, and all members of the household over

18 years of age interviewed) sampling technique, with questionnaires filled in via face-to-face interviews using laptop computers. In the first stage, the sample is selected from clusters made up of an average of 100 households. The second stage uses address sampling to systematically determine the selection from this sample. Using this technique, all localities within Turkey's borders and all citizens over the age of 18 are represented (excluding 'institutional populations' eg, those in hospitals, hotels, army barracks etc.) [31].

As well as health–specific questions, a number of demographic details and satisfaction with other public services are recorded from respondents meaning these can be controlled for at the individual–level when analyzing the data. **Table 2** shows the number of respondents each year of the survey, with a total sample of $n = 62\,933$ in the nine annual surveys undertaken between 2003 and 2012 that coincide with the health system reforms.

The question used as the outcome measure for the analyses was: "Satisfaction with health care services?", with five possible responses of: 1) Very satisfied; 2) Satisfied; 3) Medium; 4) Not satisfied; 5) Not at all satisfied.

Using the factors affecting user satisfaction with health services identified in the literature (**Table 1**), data was extracted from the LSS. Multivariate logistic regression analysis was used to control for the influencing individual characteristics available in the data. The health service satisfaction question shown above was changed to a binary 'satisfied' (combining 1 and 2 from the above)/ 'unsatisfied' (combining 3, 4 and 5 from the above) variable for ease of analysis, and used as the outcome measure in the regression model.

Table 2. Sample size of Life Satisfaction Survey, by ye	eai
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Year	SAMPLE SIZE OF THE SURVEY
2004	6714
2005	6983
2006	6432
2007	6442
2008	6465
2009	7546
2010	7027
2011	7368
2012	7956

The independent variables included based on the available data were: year; age; gender; urban/rural; education; household income (socioeconomic status); services used in previous year (in order to assess relative satisfaction with type of service used); satisfaction with own health (as a proxy for self–assessed health status); and satisfaction with other services (as a proxy for psychological factors ie, general 'satisfaction disposition' of the individual).

The basic model being tested in the study is therefore:

 $y_1 = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 = \beta_6 X_6 + \beta_7 X_7 + \beta_8 X_8 + \beta_9 X_9 + \epsilon_1$

where $y_i = \text{Satisfaction}$ with health care services, $\alpha = \text{Constant}$, $X_1 = \text{Satisfaction}$ with own health, $X_2 = \text{Age}$, $X_3 = \text{Gender}$, $X_4 = \text{Urban/Rural}$, $X_5 = \text{Educational}$ level, $X_6 = \text{Service}$ used, $X_7 = \text{Household}$ income, $X_8 = \text{Satisfaction}$ with other services, $X_9 = \text{Year}$, $\beta_i = \text{Coefficient}$, $\varepsilon_i = \text{Error}$.

The "satisfaction with other services" variable is a mean of binary satisfaction variables for satisfaction with: public security, criminal prosecution, education, social security, transportation, and general operations of public services, for each individual.

The regression model was run including only those who had used health services in the previous year (n=43143) in order to ensure the satisfaction measure matched to the year attributed to it.

RESULTS

Over the period of the HTP reforms, a number of changes occurred in access to the health system, and where people chose to seek care. **Figure 1** shows increasing use of health services in general over the 9–year period, with an almost 20% rise in those reporting having used health services over the time period shown.

Increased access, shown by the insurance coverage over this same time period (**Figure 2**), is a likely contributor to this increased use.

Increased access and subsequent use of health services were accompanied with changes of providers where patients

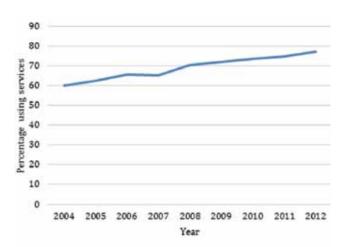


Figure 1. Percentage of survey respondents reporting having used any health services in the past year.

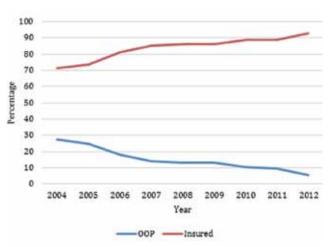


Figure 2. Percentage of respondents covered by health insurance or uninsured and paying out–of–pocket for health expenditures (by year, 2004–2012).

sought their first–contact with the health system. **Figure 3** shows the changes in choice of public or private health sector, and the proportion choosing public primary care services or public secondary care as their first point of contact.

Within this context of increased use of services and changing patterns of use of the different service types, we see changes in satisfaction with the health services being used.

Figure 4 shows trends for satisfaction levels. General satisfaction with all health services has improved steadily between 2006 and 2012, over the years of reforms, with the most rapid change occurring in the earliest years of data available for the 'last use of service' variable (between 2006 and 2007).

When the factors that affect user satisfaction with health services (**Table 1**) were controlled for using the multivariate regression model, the increases in satisfaction observed over the years holds true. Results from this model can be

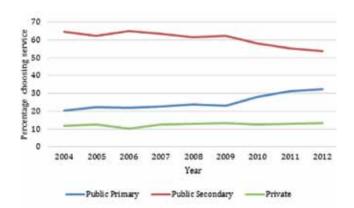


Figure 3. Proportion of those who would choose each service type for first–contact with health services.

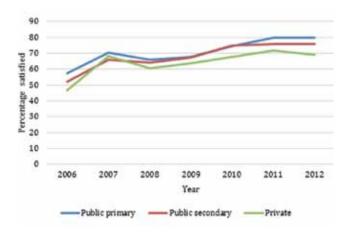


Figure 4. Satisfaction with health services by most recent service use and by year.

seen in **Table 3**. There was a significant (P < 0.001) increase in user satisfaction with health services in almost every year (bar 2006) from the baseline measure. In 2012, the odds of being satisfied with health services was 2.56 (95% confidence interval (CI) of 2.01–3.24) times that in 2004, having peaked at 3.58 (95% CI 2.82–4.55) times the baseline odds in 2011.

Trends in the adjusted odds ratios (ORs) of the other variables agree with findings from published literature (**Table 1**). Interestingly, the above results indicate that those who used public primary care services were slightly, but significantly (P<0.05) more satisfied than those who used any other services.

To explain this increased satisfaction with primary care services, satisfaction with key aspects of service delivery were examined. **Figure 5** shows issues people had when using particular services. The quality of all services as perceived by the respondents appears to be improving over the years. Private and public primary care services appear to be the

services people have the least problems in relation to perceived quality. These are also the services with which people are most satisfied with the providers.

These quality indicators can probably help account for the increased satisfaction with public primary care services, and the increase in seeking first–contact with these providers.

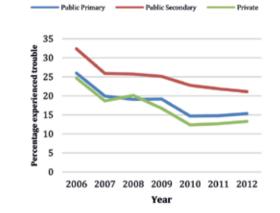
The main reason identified by the respondents for choosing a private provider as the provider of first-contact service was satisfaction with the service, although the level of satisfaction remained around 60-65% between 2004 and 2012. Conversely, necessity as a reason declined over time from 25% to less than 10%, whereas proximity as a reason increased from 10% to almost 20% (Figure 6). The main reasons for choosing public primary care providers as the provider of first-contact service was closeness of the service, increasing from around 50% in 2004 to almost 70% in 2012. Necessity as a reason declined from more than 40% in 2004 to less than 10% in 2012. Conversely, satisfaction with services as the reason for choosing public primary care providers increased over time from around 5% in 2004 to almost 20% in 2012. While necessity was the main reason (more than 80%) for choosing a public secondary care provider in 2004, by 2012 this had declined to around 30%, while satisfaction with services and closeness of the services increased from less than 5% for both to around 30%.

The trends shown in **Figure 6** suggest that necessity as the main reason for choosing a specific service type is decreasing steadily. Respondents are increasingly choosing a particular type of service because they are satisfied with the service provided, particularly when choosing to use private care. Geographic accessibility as a reason is increasing for all services, reflecting the increasing availability and proximity of each type of provider as a result of the reforms and the ability of citizens to choose health care providers.

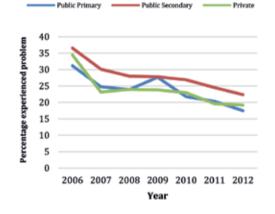
DISCUSSION

The findings show that the user satisfaction with health services has increased significantly (P < 0.001) in Turkey over the period of HTP reforms, the implementation of which began in 2003, with scaling up of the new family medicine centered primary health care model from 2006 onwards. The statistically significant increase in user satisfaction levels holds after controlling for demographic factors, which also influence user satisfaction.

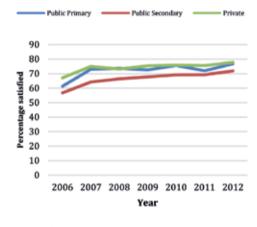
Similar directions of effect, as detailed in the earlier published literature, were found for each of the demographic factors analyzed. For example, those who were most satisfied with other public services (used as a proxy for psycho– social determinants) were much more likely (adjusted OR=4.43 (95%CI 4.23–4.64)) to also be satisfied with



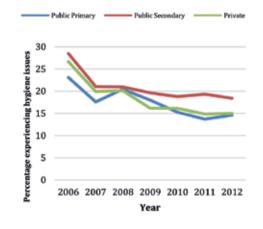
Experiencing trouble getting an appointment, by year



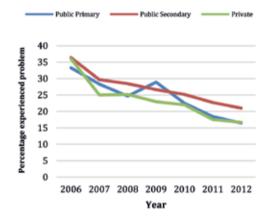
Experiencing problems with physician behavior, by year



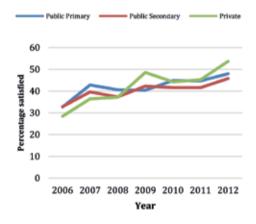
Satisfied with service received by year



Experiencing cleaning/hygiene issues, by year



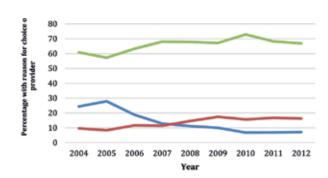
Experiencing problems with nurses/orderlies behavior, by year



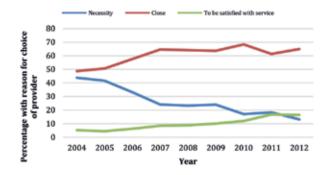
Satisfied with doctor and health care provider numbers, by year

Figure 5. Experience of respondents in relation to quality factors.

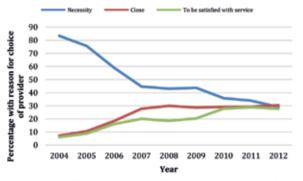
health services. This measure is not commonly included in analyses of user satisfaction with health systems, but the large effect found in this study shows the importance of controlling for this factor in future studies when possible. The rise in satisfaction levels is observed in the wake of large increases in overall use of health services over the period 2004–2012), and the observed trend which suggests strongly that with the choice they have, the citizens are in-



Reasons for choosing first-contact with private care services, by year



Reasons for choosing first-contact with public primary care services, by year



Reasons for choosing first-contact with public secondary care services, by year

Figure 6. Reasons for choosing private sector, public primary care or public secondary care as the first point of contact provider.

creasingly choosing primary care services rather than secondary care services as the provider of first contact.

The steepest increase in satisfaction can be seen early on in the reforms from 2006 following the nationwide implementation of the HTP). The early period of the reforms in 2004–2007 were the years when health insurance coverage for the poor citizens and access increased most rapidly, as seen in **Figure 2**. The elimination of costs for ambulance services, and threat of detention at a hospital with non– payment [5] would likely have also contributed to (at least perceived) accessibility of health services. Furthermore, the rapid increase in the scale and scope of services, which ensured nationwide expansion of provision of comprehensive services to cover the whole country, but especially the most needy citizens (through the Green Card scheme), and the incentives for deprived pregnant women and for children [1] through the conditional cash transfer schemes to use health services, would likely have influenced utilization and satisfaction levels.

Early in the health system reform, in 2004, HTP introduced for all citizens the right to directly choose health care providers in both the public and the private sectors, which had contracts with the Social Insurance Organization to provide health care services to those insured by the general health insurance scheme. With the rapid expansion of the new family medicine model, which was rolled out nationwide by 2010, the number of primary health care services available for citizens to choose increased. Earlier studies suggest that increases in access to and use of primary care services are associated with a rise in user satisfaction levels [28]. Similarly, having a choice of provider is also associated with increased satisfaction with health services [16,23].

Figure 6 highlights the reasons for the increased satisfaction with primary care services, where patients report fewer problems with health service quality and report greater levels of satisfaction with the health services received.

We report data from 2006 to 2012, as data on specific health service use were not collected until then, limiting the period of analysis possible, but the period of analysis coincides with the scale up of family medicine centered primary care services. The lack of a regional identifier at province level has limited our ability to specifically analyze the effects of PHC on user satisfaction as the FM model was gradually rolled out across the country, but we were able to use the nationally representative annual survey data to ascertain effects of the national expansion of the FM model (**Box 1**).

The main aims of HTP were to extend health insurance to all citizens through government financing of the Green Card scheme, and by consolidating the five parallel insurance/financing schemes into a unified general health insurance, expanding access to health services, especially to primary health care, and thereby promote UHC. In addition, HTP also introduced for the citizens of Turkey the choice of health care providers, thereby improving the responsiveness of the health system to the users. Collectively, these changes, briefly summarized in Box 1, contributed to increased user satisfaction with the health system. The government regularly used the Life Satisfaction Survey to assess the perceptions of the citizens of the health system reforms and to fine-tune the reforms so as to improve the responsiveness of the health system to users and meet their expectations [1]. This ongoing learning is an important lesson for future health system reforms in Turkey and for

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Table 3. Results of the multivariate logistic regression of satisfaction with health care services (n = 43143 users of health services: 2004 to 2012 survey respondents)

	% IN POPULATION	% SATISFIED WITH HEALTH SERVICES	Crude OR (95% CI)	Adjusted OR (95% CI)
Satisfaction with own health:				
Very satisfied/Satisfied	59.06	70.03	1	1
Medium	20.68	59.67	0.63 (0.60–0.67)†	0.56 (0.53–0.59)†
Not satisfied	16.97	57.71	0.58 (0.55–0.62)†	0.48 (0.45–0.51)†
Not at all satisfied	3.29	50.70	0.44 (0.40–0.49)†	0.35 (0.31–0.39)†
Age:				
18–34	32.99	58.92	0.83 (0.79–0.88)†	0.83 (0.79–0.88)†
35–49	30.55	63.23	1	1
50–64	22.81	69.64	1.33 (1.26–1.41)†	1.28 (1.20–1.37)†
65+	13.65	77.09	1.96 (1.82–2.10)†	1.86 (1.72–2.02)†
Gender:				
Male	38.87	64.31	1	1
Female	61.13	65.70	1.06 (1.02–1.11)†	1.14 (1.08–1.20)†
Urban/Rural:				
Urban	72.24	63.07	1	1
Rural	27.76	70.61	1.41 (1.34–1.47)†	1.19 (1.13–1.26)†
Education:				
Illiterate	12.67	70.94	1	1
Primary education	51.40	69.39	0.93 (0.87–0.99)*	0.79 (0.73–0.85)†
Secondary education	27.38	59.18	0.59 (0.55–0.64)†	0.52 (0.47–0.57)†
University education	8.55	50.31	0.41 (0.38–0.45)†	0.44 (0.39–0.50)†
Use of services:				
Other	19.97	51.20	1	1
Public primary	15.08	72.24	2.48 (2.32–2.66)†	1.26 (1.01–1.58)*
Public secondary	51.23	68.53	2.08 (1.97-2.18)†	1.15 (0.92–1.43)
Private care	13.73	65.13	1.78 (1.66–1.91)†	1.16 (0.93–1.46)
Household income:				
Lowest bracket	18.26	68.58	1	1
Lower middle bracket	24.34	68.90	1.02 (0.95–1.08)	0.93 (0.86–0.99)*
Middle bracket	21.30	66.06	0.89 (0.84–0.95)†	0.87 (0.81–0.94)†
Higher middle bracket	19.98	62.44	0.76 (0.71–0.81)†	0.88 (0.82–0.95)*
Highest bracket	16.12	57.83	0.63 (0.59–0.67)†	0.90 (0.82-0.98)*
Satisfaction with other services:				
Unsatisfied	49.25	47.94	1	1
Satisfied	50.75	81.88	4.91 (4.70–5.13)†	4.43 (4.23–4.64)†
Year:				
2004	9.17	46.66	1	1
2005	9.85	54.82	1.39 (1.27–1.51)†	1.74 (1.58–1.91)†
2006	9.63	52.00	1.24 (1.13–1.35)†	1.25 (0.99–1.58)
2007	9.64	66.88	2.31 (2.11–2.52)†	2.24 (1.77–2.84)†
2008	10.42	63.65	2.00 (1.83–2.18)†	2.05 (1.62-2.60)†
2009	12.51	66.59	2.28 (2.09–2.48)†	1.98 (1.56–2.50)†
2010	11.91	73.51	3.17 (2.90–3.46)†	2.83 (2.23–3.59)†
2011	12.67	75.86	3.59 (3.29–3.92)†	3.58 (2.82-4.55)†
		19.00	0.01 (0.1=1 0.11=) (0100(=10= 1100);

OR – odds ratio, CI – confidence interval

*Significant at P<0.05.

†Significant at *P*<0.001.

countries undertaking health system reforms to achieve UHC. Nationally representative, consistent and rigorous surveys of user satisfaction at the start of and through implementation of health system reforms is very rare, and has been found lacking in most health system reforms [17,32].

Annual surveys of user perceptions of health system reforms using a nationally representative sample in Turkey provides an example of good practice that incorporates assessment and evaluation tools to provide evidence and inform implementation of reforms.

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<u>.</u>

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(PLANET)

Improving health aid for a better planet:

The planning, monitoring and evaluation tool

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Background International development assistance for health (DAH) quadrupled between 1990 and 2012, from US\$ 5.6 billion to US\$ 28.1 billion. This generates an increasing need for transparent and replicable tools that could be used to set investment priorities, monitor the distribution of funding in real time, and evaluate the impact of those investments.

Methods In this paper we present a methodology that addresses these three challenges. We call this approach PLANET, which stands for planning, monitoring and evaluation tool. Fundamentally, PLANET is based on crowdsourcing approach to obtaining information relevant to deployment of large-scale programs. Information is contributed in real time by a diverse group of participants involved in the program delivery.

Findings PLANET relies on real-time information from three levels of participants in large-scale programs: funders, managers and recipients. At each level, information is solicited to assess five key risks that are most relevant to each level of operations. The risks at the level of funders involve systematic neglect of certain areas, focus on donor's interests over that of program recipients, ineffective co-ordination between donors, questionable mechanisms of delivery and excessive loss of funding to "middle men". At the level of managers, the risks are corruption, lack of capacity and/or competence, lack of information and /or communication, undue avoidance of governmental structures / preference to non-governmental organizations and exclusion of local expertise. At the level of primary recipients, the risks are corruption, parallel operations / "verticalization", misalignment with local priorities and lack of community involvement, issues with ethics, equity and/or acceptability, and low likelihood of sustainability beyond the end of the program's implementation.

Interpretation PLANET is intended as an additional tool available to policy-makers to prioritize, monitor and evaluate large-scale development programs. In this, it should complement tools such as LiST (for health care/interventions), EQUIST (for health care/interventions) and CHNRI (for health research), which also rely on information from local experts and on local context to set priorities in a transparent, userfriendly, replicable, quantifiable and specific, algorithmic-like manner.



The last two decades have brought revolutionary changes in global health, driven by popular concern over AIDS, reemergence of tuberculosis, novel pandemics of infectious diseases (such as SARS, influenca A(H1N1)pdm09 virus and MERS CoV), the rising burden of non-communicable diseases and falling but still unacceptably high maternal and child mortality [1]. International development assistance for health (DAH) quadrupled between 1990 and 2012, from US\$ 5.6 billion to US\$ 28.1 billion, with the private and voluntary sectors taking on an increasing share of the commitment [2]. Influential philanthropic organizations (eg, Bill and Melinda Gates Foundation) and disease-specific public-private partnerships (eg, Global Fund to Fight AIDS, Tuberculosis and Malaria) have reformed the architecture of global health funding [3]. This generates an increasing need for transparent, fair, replicable and coordinated processes and tools that could be used to direct global health funding. The key challenges are setting investment priorities, monitoring the distribution of funding in real time, and evaluating the impact of these investments.

Currently, policy-makers have access to two types of information to assist with these three tasks. The first type is rooted in epidemiology and focuses on understanding the present burden of disease and the reduction in that burden (ie, morbidity and mortality) that a project or policy could achieve. Most recently, the 'lives saved' terminology has been adopted by agencies such as the Global Fund and used to drive evidence-based health policy [4]. To support this, resources have been invested (eg, by the UN agencies and the Institute for Health Metrics and Evaluation (IHME) at the University of Washington-Seattle) in generating more comprehensive and detailed estimates of global, regional and national disease burden and in getting this information into the hands of decision-makers [5]. While successful at identifying the major causes of morbidity and mortality, the focus on the burden of disease as the dominant criterion for priority setting has been criticized [6].

The second type of available information is economic and focuses largely on cost-effectiveness. Policy makers at the national and sub-national level have limited resources for scaling up cost-effective health interventions in their populations [7]. When planning the "best buys" for committing their resources, they are faced with a complex task. They need to choose among at least several dozen interventions that target various diseases and vulnerable populations and decide on the most rational way to invest in the scale up of selected health interventions. Health investors usually like to know how many deaths (or episodes of disease) could be averted for a fixed level of investment. The more deaths averted per fixed investment, the more costeffective the scale up. When the cost is low and the number of averted deaths high the intervention scale-up is highly cost–effective. When the cost is high and the number of averted deaths low then the intervention scale–up is not cost–effective. This type of analysis has been promoted by the World Bank, the Commission on Macroeconomics and Health and the recent report "Global Health 2035" [8–10].

While the above epidemiological and health economic approaches should, in theory, result in better–informed decisions, there may be a large gap between theory and practice. In some circumstances, sound epidemiological and health economic arguments may not result in successful project outcomes due to problems related to the mechanisms of delivery. For example, most DAH projects fail to align with the principles of the Paris Declaration and the Accra Agenda for Action, which outline best practice approaches to aid effectiveness [11].

The complexity and technocratic nature of both burden of disease and cost-effectiveness exercises have often led to evaluations being conducted in an opaque manner and not in line with these best practice principles. These types of analyses are often unstandardized, subjective (given the huge variation in quality and type of data), time–intensive, costly and not replicable. In this article we attempt to overcome these problems by proposing a novel approach to planning, monitoring and evaluation of development assistance for health.

PROPOSING PLANET TOOL

We present a new methodology called PLANET (Planning, Monitoring and Evaluation Tool) that could be used to improve information on the delivery and implementation of DAH. Fundamentally, PLANET is based on a combination of two useful procedures: (i) the reduction of the multi–dimensional space of a complex system to a smaller number of core variables that capture most of the variation (eg, using a statistical procedure known as principal component analysis); and (ii) the use of collective knowledge for decision– making [12,13]. Our approach brings transparency, inclusiveness, fairness and replicability to the process.

Principal component analysis is a statistical technique which reduces a very complex system of large number of variables to a small number of relatively independent "principal components" which still capture a sizeable proportion of variation in the system [13]; by defining a set of 15 "criteria". Through this the PLANET process effectively reduces a notoriously complex and multi–dimensional task, which could be approached through an almost infinite number of "lenses", into an exercise in which 15 of the most important (and reasonably independent) criteria for priority setting are clearly defined. If necessary these can later be weighted according to their relative importance to the users.

Collective knowledge has been increasingly recognized as a way to address these types of challenges [12]. Collective knowledge and crowdsourcing refer to the process of taking into account the collective input of a group of individuals rather than of a single expert (or small number of experts) to answer a question [12]. This is based on the observation that the average of collective judgments is closer to the truth than any single expert judgment in most circumstances [12]. The pre-requisites for this process to work are: (i) diversity of opinion (each person should have private information even if it is just an eccentric interpretation of the known facts); (ii) independence (people's opinions are not determined by the opinions of those around them); (iii) decentralization (people are able to specialize and draw on local knowledge); and (iv) aggregation (some mechanism exists for turning private judgments into a collective decision - in this case, the PLANET method) [12]. Once each individual is given an opportunity to express their opinion in a way that is treated equally with respect to the opinion of any other individual, then the personal biases that those individuals bring into the process tend to cancel and dilute each other regardless of who the participants are. What is left is information based on the accumulated knowledge, lifetime experience and common sense of those who took part. This collective knowledge illustrates that disagreement and contest, rather than consensus and compromise, among independent minds can lead to the best decisions [12].

CONCEPTUAL FRAMEWORK

We conceptualize DAH as a process in which multiple stakeholders invest a finite sum of money each year into improving health and development in low and middle-income countries. In theory, if the total sum was known, if it was all coordinated centrally, and if appropriate evidence on the "architecture" of missed development potential was available globally, then there would be one optimal way to invest these resources with the maximum possible impact, while all other approaches would achieve a lesser improvement in global development. In this process, the funding can be thought of the "energy" or "resource" required to fill the gaps in development, while all steps through which these funds need to be taken during this process can be seen as potentially retarding forces which may cause deviations from the most effective approach. These forces do not disappear even if more money is injected into the system. A problem is that, in reality, we neither have the detailed evidence nor the information required for the optimization of the process of DAH, nor can we monitor and centrally coordinate the flows of funding.

However, regardless of that, we can develop a conceptual framework that can systematically define all the fundamen-

tally important retarding forces that are at work through this process, and try to assess, for each initiative (based on the collective knowledge of the persons most closely informed about each step in the process), how likely it is to complete its mission, and how vulnerable it is to retarding forces (**Figure 1**).

Building on McCoy et al 2009 [14], we identify three functions associated with DAH and the associated stakeholders. The first function is labeled 'providing' and is concerned with the need to raise or generate funds (the funders of DAH) to improve global health through development. The second function is 'managing' and is concerned with the management or pooling of those funds, as well as with mechanisms for channeling funds to recipients (the managers of DAH). The third function is 'spending' and is concerned with expenditure and consumption of those funds (the recipients of DAH). It is worth noting that while this schematic establishes a clear time sequence of the key events in the DAH process, several actors work across all three levels simultaneously. Nevertheless, similar to McCoy et al. 2009 [14], we believe that these categories provide a useful framework for studying the DAH process.

FUNDERS OF DEVELOPMENT ASSISTANCE FOR HEALTH GRANTS

The first level of stakeholders of interest are the funders of DAH, referred to here as donors, which could include philanthropists, government or international organizations, and the investors from the private sector and industry. Donors have become increasingly aware of the importance of measuring success in terms of political sustainability but have not been in possession of a clear framework or technology to help them undertake this task effectively. Often their priority is on disbursing resources according to internal interests, or they find delivery data too difficult to collect accurately, or too politically sensitive (**Figure 2**).

At the level of donors, several factors could hinder the effectiveness of investments. First, donors could misalign the size of their support (financial commitment) with the size of the problem (burden of disease). An unprecedented amount of money is being pledged and used to fund health services throughout the world. However, several studies have shown that funding does not correspond closely to burden [2]. For example, Shiffman demonstrates that within communicable diseases for the years 1996 to 2003, there were several neglected topics such as acute respiratory infections and malaria [15]. Similarly, Sridhar & Batniji noted that in 2005, funding per death varied widely by disease area from US\$ 1029.10 for HIV/AIDS to US\$ 3.21 for noncommunicable disease [16]. The reasons for this misalignment could be due to the social construction of the problem [17], lobbying by vested interests [18] or the personal

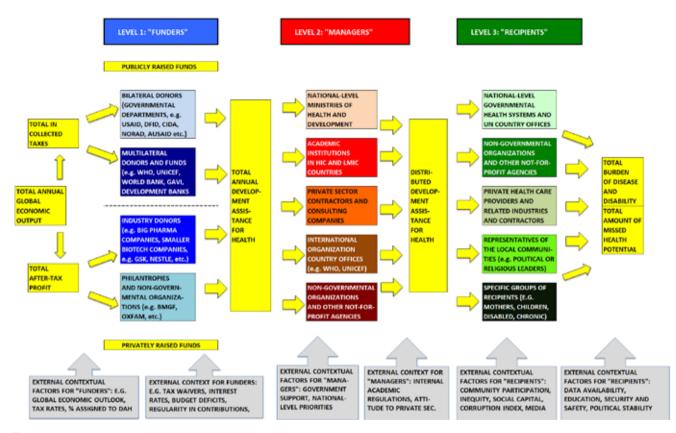


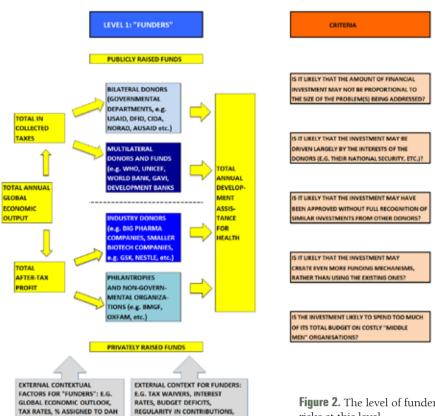
Figure 1. A summarized overview of the structure and some key determinants of function of the global development assistance system.

interests of donors [19]. Thus, the risk that the donors are misaligning their financial commitment to a disease area with the burden it causes needs to be assessed.

Second, donors could prioritize initiatives that focus on their national self-interest rather than those that support improved health in the recipient country. For example, since the Oslo Declaration in 2006, health and foreign policy have become increasingly linked [20]. While translating health into national security language might attract attention from high levels of government, this focus has been limited to a few high-profile problems such as AIDS, pandemic influenza and humanitarian assistance and not expanded to less glamorous areas such as health systems, malnutrition or water and sanitation [21]. In fact a review of six countries' policies illustrates that most strategies tend to be catalyzed and supported by concern with surveillance and control of infectious disease [22]. Thus, the risk that a development project serves national self-interests, such as economic, geopolitical or security, rather than improved health outcomes in the recipient country needs to be established.

Third, donors could fail to coordinate their activities. The current architecture of funding of global health and development is characterized by fragmentation, lack of coordination and even confusion as a diverse array of well–funded and well-meaning initiatives which descend with good intentions on countries in the developing world [23]. However ambitious or well-intentioned these initiatives might be, it becomes difficult in this environment for recipient governments to develop and implement sound national plans for their country. While there is, in general, little incentive for various development partners to coordinate their activities, some development projects work better through a joint strategy. *Thus, the risk that development partners will fail to coordinate their activities for a specific project needs to be established*.

Fourth, donors could invest in new players and models rather than strengthening and building on the existing institutional infrastructure. As noted above, there has been a continuous expansion in the number as well as type of actors involved in DAH. Instead of examining how the existing institutional infrastructure –specifically the WHO and World Bank – can be reformed to deliver on projects, new initiatives are launched that attempt to compensate for their shortcomings [24]. For example, the World Bank has an important role to play in DAH given its long history working in countries through governments, as well as in its knowledge–bank role. Similarly the WHO is unique in being governed by 193 member states and its role in setting



evidence–based norms on technical and policy matters, highlighting best practices that improve health globally and monitoring and coordinating action. *Thus, the risk that a development project will result in a new institution rather than working through the existing institutional infrastructure needs*

Finally, donors could fund their initiatives in a way that results in too much funding going to more costly institutions. As McCoy et al. discuss, global health is a multi-billion dollar industry, and there are clearly competing interests amongst different actors to make use of this funding [14]. For example, pharmaceutical companies appear to benefit considerably from global health programs that emphasize the delivery of medical commodities and treatments. NGOs, global health research institutions and UN bureaucracies also have an interest in increasing or maintaining their level of income and thus tend to prefer that funding from major donors flows through them (as managers of funding), rather than directly to developing countries. Further scrutiny is needed on aid flows in global health to assess whether they are being captured by vested interests and used to support inappropriate spending on the private commercial sector or on a large and costly global health bureaucracy and technocracy. Thus, the risk that a development project will be designed in a way that results in too much funding going to costly organizations needs to be established.

Figure 2. The level of funders and key performance risks at this level.

MANAGERS OF DEVELOPMENT ASSISTANCE FOR HEALTH GRANTS

The second level of stakeholders in DAH consists of the managers of DAH grants. These could be national government ministries, NGOs, academic institutions in donor or recipient countries, private sector (with pharmaceutical companies and biotech industries), various private or not–for–profit independent consultants and country offices of international organizations. Managers are often torn between global priorities, specifically the priorities of donors, and being accountable to local communities and the ultimate recipients of aid (**Figure 3**).

At the middle level, several factors can hinder the effectiveness of investments. First, managers could deliberately steal resources from the investment for their own benefit, ie, the risk of corruption. The need to identify and address corruption and weak governance is often lost in the commitment to raise funds and expand services [25]. *Thus, the risk that funding from the project will be stolen needs to be assessed.*

Second, managers could inadvertently channel resources to purposes other than project objectives because of miscommunication, lack of competence, or lack of capacity [26]. For example, those managing the project may not have the necessary technical or administrative skills to meet key objectives. *Thus, the risk that managers inadvertently channel resources to purposes other than project objectives due to lack of competence needs to be assessed.*

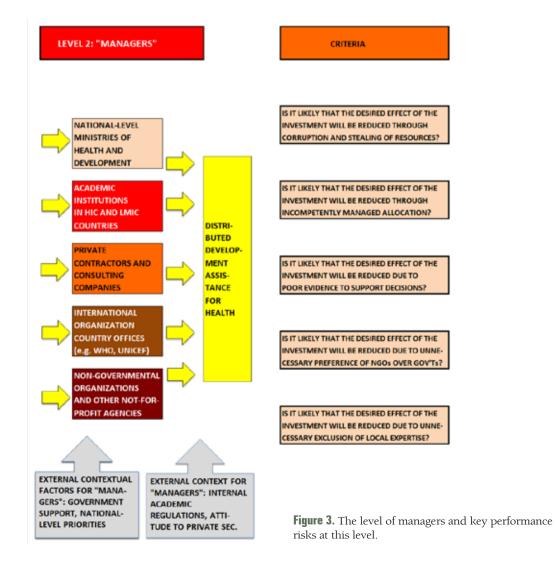
to be established.

Third, managers could lack credible information and evidence to maximize the cost–effectiveness of investments. The basis of cost–effectiveness is that interventions should not only have established effectiveness in reducing disease burden but also represent an effective use of resources. For a certain budget, population health would then be maximized through choosing interventions that show the best value for money. Most information about cost–effectiveness, such as that generated through the WHO–CHOICE project, are available at the regional level [27]. This creates challenges when applying these estimates to country and district level projects. *Thus, the risk that managers lack good information on the cost–effectiveness of investments needs to be assessed.*

Fourth, managers could route funding through non–governmental organizations or private sector bodies rather than working through governments. In the past two decades there has been a move towards funding non–state actors, especially by the newer funding institutions [23]. For example, the Global Fund's use of country–coordinating mechanisms gives a larger voice to civil society as it is supposed to include a wide range of actors in a participatory process. The US government, particularly through its HIV/AIDS funding, predominantly funds faith–based organizations and NGOs. The marginal involvement of developing country governments in many DAH projects raises questions about long–term sustainability [28]. However, in some situations funding through NGOs or private sector bodies rather than through governments can work better but this should be carefully considered over a long term time horizon. Therefore, the risk that a project routes funding through nongovernmental organizations or private sector bodies rather than through government needs to be assessed.

Fifth, managers could exclude the participation of local experts and the inclusion of local evidence in the processes of priority setting. Managers face strong incentives to orient 'upwards' towards the donors that are funding the project [29]. They have little incentive to include local experts and local knowledge. *Thus the risk that local experts and local evidence are excluded in the processes of priority setting needs to be assessed.*

The above are the first ten PLANET criteria to evaluate an initiative on DAH. The informants for these aspects would include policy-makers in various global health institutions



as well as health economic, governance and health systems experts (**Table 1**).

RECIPIENTS OF DEVELOPMENT ASSISTANCE FOR HEALTH GRANTS

The third level of stakeholders includes all those involved in the final stage of DAH of reaching the recipients (ie, government health systems, NGOs, private health care providers, local community representatives, and recipient groups (eg, mothers and children) themselves, including the operational workforce. At this level, several factors could hinder the effectiveness of investments (**Figure 4**).

First, the primary recipient could deliberately steal funding or commodities from this process for his/her own benefit.

Numerous studies have documented such problems, for example, in the procurement of health supplies, in under–the–table payments for services, and in nurses and doctors who fail to show up at their clinics but nonetheless collect their salaries [30]. *Thus, the risk that funding from the project will be stolen needs to be assessed.*

Second, the recipient could set up unnecessary parallel structures to deliver on the project rather than working through government or 'horizontally'. Horizontal interventions are defined as those that strengthen the heath care system, improve health systems service and delivery, and address general non–disease specific problems such as health worker shortages and stock outs of medicines and supplies [31]. Despite the consensus that DAH should be funded horizontally, most financing is channeled vertically

Table 1. Questionnaire for Implementation of PLANET

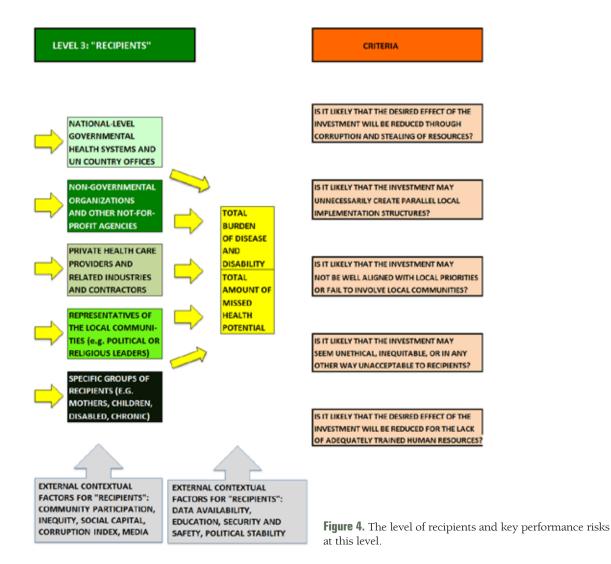
LEVEL	Planning	Monitoring	Evaluating
1 – Donors	 Is it likely that the amount of financial investment may not be proportional to the size of the problem(s) being addressed? 	 Is the amount of financial investment dis- proportional to the size of the problem(s) being addressed? 	 Was the amount of financial invest- ment disproportional to the size of the problem(s) being addressed?
	2. Is it likely that the investment may be driven largely by the interests of the do-nors?	2. Is the investment driven largely by the in- terests of the donors?	2. Was the investment driven largely by the interests of the donors?
	3. Is it likely that the investment may have been approved without full recognition of similar investments from other donors?	3. Is the investment being implemented without full recognition of similar invest- ments from other donors?	3. Was the investment approved without full recognition of similar investments from other donors?
	4. Is it likely that investment may create even more funding mechanisms rather than using existing ones?	4. Is the investment creating even more funding mechanisms rather than using existing ones?	4. Did the investment create even more funding mechanisms rather than using existing ones?
	5. Is the investment likely to spend too much of its total budget on costly 'middle men' organizations?	5. Is the investment spending too much of its total budget on costly 'middle men' or- ganizations?	5. Did the investment spend too much of its total budget on costly 'middle men' organizations?
2 – Managers	1. Is it likely that the desired effect of the investment will be reduced through corruption and stealing of resources?	1. Is the desired effect of the investment be- ing reduced through corruption and steal- ing of resources?	 Was the desired effect of the investment reduced through corruption and steal- ing of resources?
	2. Is it likely that the desired effect of the investment will be reduced through incompetently managed allocation?	2. Is the desired effect of the investment be- ing reduced through incompetently man- aged allocation?	2. Was the desired effect of the investment reduced through incompetently man- aged allocation?
	3. Is it likely that the desired effect of the in- vestment will be reduced due to poor ev- idence to support decisions?	3. Is the desired effect of the investment be- ing reduced due to poor evidence to sup- port decisions?	3. Was the desired effect of the investment reduced due to poor evidence to sup- port decisions?
	4. Is it likely that the desired effect of the investment will be reduced due to unnecessary preference for NGOs over government?	4. Is the desired effect of the investment be- ing reduced due to unnecessary prefer- ence for NGOs over government?	4. Was the desired effect of the investment reduced due to unnecessary preference for NGOs over government?
	5. Is it likely that the desired effect of the investment will be reduced due to unnecessary exclusion of local expertise?	5. Is the desired effect of the investment be- ing reduced due to unnecessary exclusion of local expertise?	5. Was the desired effect of the investment reduced due to unnecessary exclusion of local expertise?
3 – Recipients	1. Is it likely that the desired effect of the investment will be reduced through corruption and stealing of resources?	1. Is the desired effect of the investment be- ing reduced through corruption and steal- ing of resources?	 Was the desired effect of the investment reduced through corruption and steal- ing of resources?
	2. Is it likely that the investment may unnecessarily create parallel local implementation structures?	2. Is the investment unnecessarily creating parallel local implementation structures?	2. Did the investment unnecessarily create parallel local implementation structures?
	3. Is it likely that the investment may not be well aligned with local priorities or fail to involve local communities?	3. Is the investment not well aligned with lo- cal priorities or failing to involve local communities?	3. Was the investment misaligned with lo- cal priorities or did it fail to involve lo- cal communities?
	4. Is it likely that the investment may seem unethical, inequitable, or in any other way unacceptable to recipients?	4. Is the investment unethical, inequitable, or in any other way unacceptable to re- cipients?	4. Was the investment unethical, inequi- table, or in any other way unacceptable to recipients?
	5. Is it likely that the desired effect of the investment will be reduced due to lack of adequately trained human resources?	5. Is the desired effect of the investment be- ing reduced due to lack of adequately trained human resources?	5. Was the desired effect of the investment reduced due to lack of adequately trained human resources?

(defined as setting up separate systems to deliver on the objectives often related to specific diseases). In recent years much of the funding has been directed to address HIV/ AIDS, malaria and TB [2]. The imperative to show measurable results in a short–time frame results in setting in place short–term fixes that deliver on the project with the problem that relatively little funding may go towards capacity–building or working through government. *Thus the risk that a project will result in unjustified parallel local implementation structures rather than work through the existing health system needs to be assessed.*

Third, the project may not be aligned with local priorities or promote community involvement. The choice of a DAH priority directly affects recipients' health, meaning that these individuals should also have the right to participate in deciding on the priorities and implementation of the project [32]. If this participation is to be meaningful nationally (or locally), then the results of the participation must have the possibility of having an impact, in this case, of affecting the nature of the project. *Thus the risk that the* project will not be aligned with local priorities or promote community involvement needs to be assessed.

Fourth, the project could be seen as unethical, inequitable or unacceptable to the final recipients. In recent years policy–makers have increasingly become aware of the disparities in health status between different groups in society and the distributional impact of interventions [33]. In particular, concern focuses on the extent to which interventions reach and benefit disadvantaged groups, such as the poor, women or certain ethnicities or otherwise marginalized populations. *Thus, the risk that the project is not ethical, equitable or acceptable to the final beneficiaries needs to be assessed.*

Finally, the project may not be sustainable, defined in terms of ensuring required human resource capacity to deliver on targets and objectives. It is increasingly recognized that the success of local implementation is highly dependent on a strong health workforce [26]. Despite this awareness, much of the focus of DAH is on commodities such as vaccines and drugs. While these are of course necessary, it is people who prevent disease and administer cures. *Thus the risk that*



the project will lack the requisite human resources, such as trained health workers, needs to be assessed.

The informants reporting of these final 5 criteria could be representatives of operations workforce and / or the ultimate recipients. The above factors can be used as the 15 criteria to plan an initiative on DAH at the inception stage, to monitor its implementation in real-time, and/or to evaluate previously conducted efforts. The resulting questions that could be asked of key informants are provided in **Table 1**.

THREE APPLICATIONS OF PLANET

The PLANET approach, as defined above, has three major applications in the field of development assistance. First is in *planning* of new initiatives in development. Donors in particular might be considering different investment options and project possibilities to address problems in development. While the overarching concern is justifiably a reduction in burden of disease, running a PLANET exercise will look at other equally important dimensions that would impact on the success of the project in reducing burden of disease as well as aligning with best practice in development.

How could the framework be used? Based on this conceptual framework we have developed a questionnaire (Table 1) which can be used to engage three groups of respondents. These would include those with knowledge of health governance, economics and health systems as well as policy-makers intimately involved with the execution of the project. It would also include those at the local level who are likely to be involved with the delivery of the project as well as the actual beneficiaries. All relevant stakeholders would be given this questionnaire and asked to respond independently and anonymously based on their knowledge of the project. The process could be conducted by technical experts in a transparent way (eg, each vote counts equally). The outcome would be a comprehensive list of the strengths and weaknesses of particular projects against many criteria, based on the collective input of technical experts. Additional criterion or questions can be added or substituted in to ensure covering all aspects relevant to that specific project. Analysis of the respondent data would, taken together, provide a complete picture of the strengths and weaknesses of the project that would be made available publicly.

Given that donors would be running this exercise using the expertise and accumulated knowledge of respondents, an additional step is necessary. Donors would need to define the context of the exercise based on their anticipated outcomes, the population they are targeting, the time–frame they are working under as well as stating how much risk they are willing to take to reach certain outcomes. For example, the Bill & Melinda Gates Foundation might be willing to take a major risk for a high–payoff while public donors such as the UK government might be looking to minimize risk and under those conditions to maximize health outcomes. The outcome would be a comprehensive list with competing priorities ranked according to the combined scores they received in the process. Such a list would be helpful because it provides an overview of the strengths and weaknesses of competing DAH options against many criteria, based on the collective input of technical experts. The list can also be adjusted by taking the values of many stakeholders into account such as occurred during the extensive experience with the implementation of CHNRI in health research prioritization [34].

Second, PLANET can be used to monitor ongoing initiatives and receive real-time feedback on their implementation. Third, PLANET could also be used to evaluate the success of previous initiatives. Evaluation is often woefully neglected in development and efforts such as by the Center for Global Development to fill this gap have focused on the creation of new institutions with the capacity to undertake this kind of work [35]. However, no standardized methodology exists to evaluate projects across multiple criteria capturing the essence of whether or not it was successful. Furthermore, this approach is not only concerned with considerations of disease burden reductions or change in health outcomes but with the actual process of implementation of the project, its strengths and weaknesses and whether it aligns with 'best practice.' The implementation would be similar to that described above using a modified questionnaire (Table 1).

STRATEGIES FOR DATA COLLECTION

Exploitation of collective knowledge is now possible and moreover easier and cheaper than ever before. Information /communication technology becoming a digital utility enables us now to seek input from hundreds or thousands of independent individuals at little higher cost than asking one person. We can now, in real-time, in almost every country or setting collect feedback or opinions from an estimated 6.8 billion people who actively use mobile phones (with the proportion of smartphones rapidly growing) [36]. This can be done through text-message [37,38], automated phone calls, dedicated apps, email or the internet in a device or platform agnostic manner. It is certain that this is redefining not just the norms of who provides a feedback or communication of their assessment of a programme and how and when this is done, but also how DAH and indeed health care is delivered or consumed. The PLANET questionnaire is currently being developed into an app that would be freely available to all governments, international

institutions and individuals looking for a simple, techfriendly tool to plan, monitor and evaluate DAH.

CONCLUSION

The PLANET tool has several major advantages over existing efforts in planning, monitoring and evaluation. First, it presents a standardized methodology that can be used for planning, monitoring and evaluation of any type of DAH project, but it also has sufficient flexibility to be tailored to the context of specific projects or initiatives. PLANET would be an additional tool available to policy–makers, along with LiST (for health care/interventions) [39] and CHNRI (for health research) [13] which will involve local experts and incorporate issues of local context in the process of determining priorities in a transparent, user–friendly, replicable, quantifiable and specific, algorithm–like manner. Second, it is simple to implement and with the development of mobile–phone software, should be able to be run anywhere in the world at low–cost. The low–cost of input means it can be run multiple times resulting in real-time monitoring of DAH. Third, while respondents are protected through anonymity in feedback, the results are provided transparently. Finally, the exercise gives equal voice to all those involved in the process of development from the donor (eg, in London, Seoul or Seattle) to a manager and to a recipient (in rural Uganda, Dhaka or Antigua). The voice of local stakeholders, including operations teams and beneficiaries, is included in every exercise.

The use of these types of novel methodologies can lead to more rational planning, higher quality evaluation as well as more knowledgeable future decision—making, especially given that DAH has traditionally lacked formal tools to examine delivery and implementation. The use of such tools would promote attention to objective evidence on planning, monitoring and evaluation leading to more effective aid and ultimately better evidence on reduction in the burden of disease across the world and how this relates or could relate to specific development efforts.

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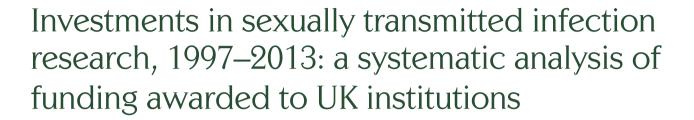
Authorship declaration: DS and IR developed the conceptual framework together. DS wrote the first draft of the manuscript. IR, JC, MC, HC and NW all provided written input and feedback into that draft.

Declaration of interest. All authors have completed the Unified Competing Interest form at www. icmje.org/coi_disclosure.pdf (available on request from the corresponding author). None of the participating authors has a conflicting financial or other interest related to the work detailed in this manuscript.

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Michael Head University College London Farr Institute for Health Informatics 222 Euston Road London NW1 2DA m.head@ucl.ac.uk **Background** We report the first study that analyses public and philanthropic investments awarded to UK institutions for research related to sexually transmitted infections (STIs).

Methods We systematically searched award data from the major funders for information on all infectious disease research funding awarded in 1997–2013. The STI–related projects were identified and categorised by pathogen, disease and type of science along the research pipeline from preclinical to translational research.

Findings We identified 7393 infection–related awards with total investment of GBP 3.5 billion. Of these, 1238 awards (16.7%) covering funding of GBP 719.1 million (20.5%) were for STI research. HIV as an STI received GBP 465 million across 719 studies; non–HIV STIs received GBP 139 million across 378 studies. The Medical Research Council provided greatest investment (GBP 193 million for HIV, GBP 45 million for non–HIV STIs). Preclinical awards totalled GBP 233 million (37.1%), whilst translational research received GBP 286 million (39.7%). Substantial proportions of HIV investment addressed global health research (GBP 265 million), vaccinology (GBP 110 million) and therapeutics (GBP 202 million). For other STIs, investments focused on diagnostics (GBP 45 million) and global health (GBP 27 million). Human Papilloma Virus research received GBP 58 million and chlamydia GBP 24 million. Funding for non–HIV STIs has declined in the three most recent years of this data set.

Conclusions The investment for HIV research awarded to UK institutions correlates with the high global burden, but other STIs are relatively neglected, including gonorrhoea and syphilis. Future STI funding should be better aligned with burden while addressing the emerging risk of antimicrobial resistance in *Neisseria gonorrhoeae* and outbreaks of other pathogens.

Sexually transmitted infections (STIs) are responsible for a large global burden of disease, of which HIV is individually the pathogen of greatest public health impact. In 2010, HIV accounted for 81.5 million disability–adjusted life years (DALYs), 3.3% of the global burden [1], whilst revised figures suggested an estimated 1.3 million deaths from HIV in 2013 [2].

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There are approximately 500 million transmissions of STIs (other than HIV) worldwide annually, whilst seroprevalence of herpes simplex virus is highest in Africa, with infection found in 30-80% of women and 10% to 50% of men [3]. In the UK, high-risk human papilloma virus infection was detected in 15.9% of women [4]. Chlamydia is the most commonly diagnosed STI in England with over 200000 new diagnoses in 2012 [5]. Stillbirth and neonatal damage due to congenital syphilis are thought to rival the early life burden of HIV infection, though arguably syphilis receives far less attention [6]. Incidence of syphilis is rising in many countries, including the UK and China [7,8]. There are over 100 million new cases of gonorrhoea globally each year [9], and incidence is also increasing in England [5]. The extent of observed antimicrobial resistance patterns has led to concerns that gonorrhoea will soon become untreatable [9,10]. Viral hepatitis and infection with Mycoplasma genitalium are further infections that add to the overall burden of STIs.

One tool in developing policies that attempt to better prevent, manage and treat all STIs is investment in research. Funding covers all types of science along the R&D research pipeline from pre-clinical to operational and implementation research. UK institutions have received an estimated GBP 2.6 billion of public and charitable funding to carry out infectious disease research between 1997 and 2010 [11], and estimates suggest the UK ranks second globally in terms of the amount of research and development (R&D) funding for neglected infectious disease research [12]. There are also 38 UK institutions in the most recent rankings list of the 'top 100 most global universities' [13]; thus there is a large quantity of research funding available for analysis coming from institutions carrying out relevant global activity. We report here on the funding for STI-related research awarded to UK institutions in 1997-2013, including three further years of investment data as part of an update on the previous work [11].

We identify probable areas of research strength and possible investment gaps in relation to global sexual health that will be of relevance to policy–makers, funders and researchers, and then briefly discuss how new approaches might help with managing burdens and allocating existing resources to the most appropriate preclinical, interventional or observation studies.

METHODS

We analysed infectious disease-related studies funded over a 17-year period (1997–2013 inclusive) and awarded to UK institutions, and identified those relevant to STI research. Global health studies were defined as those which investigated diseases not endemic in the UK, or where the study had a clear reference to another country (eg, HIV in South Africa). We excluded open–access data from the pharmaceutical industry as it was limited and not representative.

The methods have been described in detail previously [11], and also to some extent replicated on the study website [14] and in other study publications [15-17]. The overarching data set was constructed by approaching the major sources of public and charitable funding for infectious disease research studies, including the Wellcome Trust, Medical Research Council and other research councils, UK government departments, the European Commission, Bill and Melinda Gates Foundation, and other research charities. Funders were identified by searching databases such as the National Research Register (now archived, ref. [18]), or Clinicaltrials.gov, authors knowledge of the funding landscape, through the knowledge of the Infectious Disease Research Network (www.idrn.org) and through searches of the internet. Where available, the funding decisions listed on their website were searched for infectious disease research awards (eg, Wellcome Trust); otherwise, the funder was directly approached and asked to provide information on their infection-related awards.

Each study was screened for relevance to infectious disease research and assigned to as many disease categories as appropriate. These included area of microbiology (bacteriology, virology, parasitology, mycology) and cross-cutting themes such as global health and antimicrobial resistance, as well as awards relating to new tools and products such as diagnostics, therapeutics and vaccines. The categories were selected based on author discussions during and since the data set was developed. Studies were also allocated to one of four categories (initially for 1997-2010 data) along the R&D pipeline: pre-clinical; phase 1, 2, or 3; intervention and product development; and translational research. For 2011–2013 data only, a fifth category has been added, this being cross-disciplinary, and is defined as a study significantly covering two types of science along the R&D pipeline (as per our categorisation above, also see ref. [14]. This category was added in response to a seemingly increasing number of awards involving consortia or programme grants that transcend the research pipeline boundaries of this study. The 1997-2010 data has not yet retrospectively been assessed for cross-disciplinary studies (capacity for a significant retrospective analysis of the entire initial data set is limited). The major funders were considered separately, while others were grouped into categories, such as professional bodies and societies, or other research charities. A total of 26 funder categories were used. All categorisation was carried out by author MGH, with provisional data sets circulated to authors for review and comment. Author JRF further verified a random sample of 10% of the 1997-2010 data set, whilst JRF and further external colleagues carried out similar process for 2011-2013 data. Author agreement was measured by a Kappa score (0.95 and 0.91) and differences settled by consensus. We excluded studies not immediately relevant to infection, veterinary infectious disease research studies (unless there was a clear zoonotic component), and studies which included UK collaborators, but where the funding was awarded to a non-UK institution. Unfunded studies were also excluded. Grants awarded in a currency other than pounds sterling were converted to UK pounds using the mean exchange rate in the year of the award. All awards were adjusted for inflation. Relative levels of investment were presented via a 'GBP per disability-adjusted life years' (DALY) figure; this represented the total investment in research per 1 DALY. The DALY figures were extracted from the 2010 Global Burden of Disease study [1].

This analysis includes HIV as an STI. Since sexual transmission of HIV is in most settings overwhelmingly the most common route, we included HIV–related studies as STI– related unless they specifically addressed other transmission modes. Therefore, studies investigating HIV via vertical transmission or via bloodborne pathways were excluded. Similarly, where other pathogens have multiple modes of transmission, eg, hepatitis B, they were only included if transmission by sexual contact were explicitly stated in the study title or abstract. Data management was carried out in Microsoft Excel and Access (versions 2007 and 2013) and statistical analysis with Stata (version 13).

RESULTS

A total of 7393 awards were identified as relevant to all infectious diseases across 1997–2013 with a total investment of GBP 3.5 billion. Of these, 1238 awards (16.7%) were identified as relevant to STI research, with total funding of GBP 719.1 million (20.5% of all infectious disease funding; **Table 1**). Some top–level data reproduced here have been previously published as 1997–2010 results in an overview of all infectious disease funding (specifically study numbers and total funding for HIV including non–STI transmissions, gonorrhea, syphilis, chlamydia, HPV and HSV) [11]. There was one pre–clinical study in 2003 focusing on *Trichomonas vaginalis*.

Of this, GBP 596.8 million (83.0%) was related to HIV across 873 studies (70.5%), and GBP 155.6 million (21.6%) was invested in other STIs over 378 studies (32.5%). Median study funding for HIV research was GBP 173 109 (IQR GBP 39374–454 801); median study funding for other STIs was GBP 105 115 (IQR GBP 17827–251 356). A wide variety of funders contributed greatly to the sum funding, but the Medical Research Council invested the greatest amount for both HIV (GBP 192.8 million, 32.0%) and for other STIs (GBP 45.2 million, 29.0%). Annual funding is volatile with no consistent temporal trend in funding awards for either HIV or other STI research, and it appears as though funding for non–HIV STIs is declining in the most recent years of this data set (**Figure 1**).

For HIV research, pre–clinical science received GBP 247.8 million (41.5%) across 358 studies, phase I to III trials GBP 110.6 million (18.5%) across 62 studies, product development research GBP 32.9 million (5.5%) across 55 studies, and implementation and operational research GBP 194.4 million (32.6%) across 397 studies; there were also one cross–disciplinary study awarded between 2011–2013 (**Table 2**). For other STIs, pre–clinical science received GBP 35.9 million (23.1%) across 123 studies, phase I to III trials GBP 0.6 million (0.4%) across 4 studies, product development research GBP 12.0 million (7.7%) across 27 studies

Table 1. Total funding, mean and median award size of HIV and other sexually transmitted infections (STI) research awarded 1997–2013

1997=2015							
Disease	Number of studies	Percentage of STI study number (%)*	Total funding (GBP)	Percentage of STI fund- ing (%)*	Mean award, GBP (SD)	Median award, GBP (IQR)	TOP FUNDER, MILLIONS (%)
All STI studies	1238	n/a	719086641	n/a	580845 (1925725)	144138 (33247–365209)	MRC, 284.4 (39.5)
Non–HIV STIs	402	32.47	155630214	21.64	387 139 (965 424)	105115 (17827–251356)	MRC, 45.2 (29.0)
HIV	873	70.52	596800543	82.99	663534 (2213359)	173109 (39374-454801)	MRC, 192.8 (32.0)
Chlamydia	119	9.61	24 485 887	3.41	205763 (556606)	60212 (11450–180498)	UK government depart- ment, non–DH, 9.6 (39.2)
Gonorrhoea	20	1.62	1388703	0.19	69435 (96071)	13968 (3699–144980)	Wellcome, 0.46 (33.3)
Syphilis	5	0.40	1061560	0.15	212312 (152848)	207346 (113088–229907)	Wellcome, 0.57 (53.5)
Candida	87	7.03	29458307	4.10	338601 (445301)	261 386 (86 394–382 357)	BBSRC, 11.3 (38.5)
Mycoplasma	3	0.24	245667	0.03	81889 (107412)	36409 (46989–204559)	MRC, 0.20 (83.3)
HPV	164	13.25	58254838	8.10	355212 (811689)	113852 (38476–242110)	Charity, 31.9 (54.8)
Herpes Simplex Virus	10	0.81	2530037	0.35	253003 (381987)	95514 (15682–309610)	Wellcome, 2.0 (78.1)
Viral hepatitis	3	0.24	74448	0.01	24816 (24446)	13135 (8401–52911)	Other, 0.05 (71.1)

n/a – not applicable, SD – standard deviation; IQR – interquartile range, MRC –Medical Research Council

*Percentages in are calculated as a fraction of all STI research. Because awards can cover more than one disease area or product category, the sum of these column percentages do not add up to exactly 100%.

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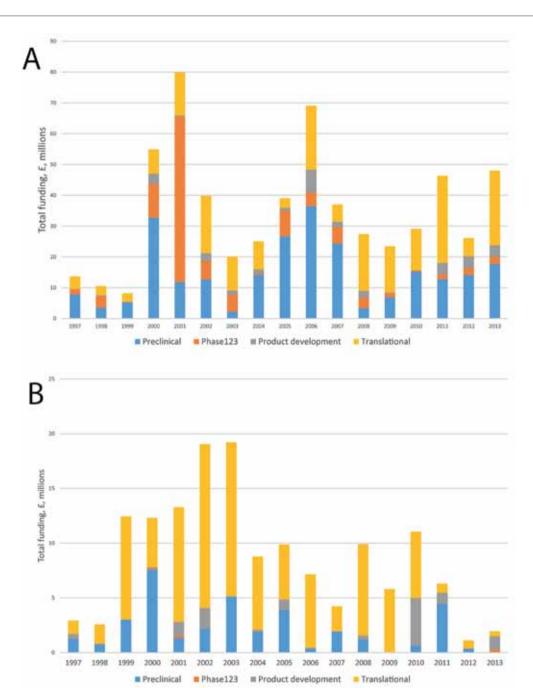


Figure 1. Investments on HIV (**A**) and other sexually–transmitted infection (**B**) research awarded to the UK over time and by type of science (x1 HIV and x2 STI cross–disciplinary studies not shown here).

ies, and implementation and operational research GBP 99.5 million (64.0%) across 246 studies; Further, there were also three cross–disciplinary studies (two for non–HIV STIs, and one for HIV research) totalling GBP 18.7 million.

Within HIV research (**Table 3**), global health–related studies received GBP 264.9 million (44.4% of HIV research) across 228 studies (across all infectious disease, studies with a clear global health component represented 36.3% of all funding). There was also GBP 109.7 million (18.4%) invested in vaccinology, GBP 202.3 million (33.9%) in therapeutics and GBP 25.2 million (4.2%) in diagnostics. For other STI research, GBP 27.2 million was concentrated on global health (17.5% of all non–HIV STI funding), across 38 studies. The main focus here was for studies relating to non–pathogen–specific STI research; despite sum funding of GBP 24.5 million, there was just one study (GBP 0.3 million) considering chlamydia in a global context

There was GBP 3.5 million (2.3%) invested in in vaccinology research, GBP 3.8 million (2.4%) for therapeutics and GBP 44.7 million (28.7%) for diagnostics. Antimicrobial resistance–related investments were GBP 20.7 million (3.5%) for HIV, and GBP 5.7 million (3.7%) for other STIs. Table 2. Funding of research into HIV and other sexually transmitted infections (STIs) 1997–2013, described by type of science

Study type	ALL STI	NON-HIV STI	HIV
Pre–clinical:			
Study numbers	461	123	358
Funding (GBP)	267 053 431	35881994	247843494
Phase I – III:			
Study numbers	62	4	62
Funding (GBP)	106983764	589207	110 562 571
Intervention & product development:			
Study numbers	79	27	55
Funding (GBP)	40749294	11967782	32 949 526
Translational:			
Study numbers	633	246	397
Funding (GBP)	285 593 246	99 542 253	194387022

Table 3. Funding of research into HIV and other sexually transmitted infections (STIs) described by general disease theme

Disease	Number of studies	Total funding (GBP)	Percentage of all HIV funding	Mean award, GBP (SD)	Median award, GBP (IQR)	TOP FUNDER, MILLIONS (%)
HIV/AIDS:						
Global health	228	264900733	44.4%	1161845 (3885828)	198934 (53409–694934)	DFID, 78.9 (29.8)
Vaccinology	70	109708029	18.4%	1567258 (2963178)	558247 (256053–1361466)	European Commission, 29.5 (26.9)
Therapeutics	184	202317448	33.9%	1099551 (4089456)	195947 (36809–672265)	European Commission, 60.1 (29.7)
Paediatrics	77	32 503 928	5.4%	422128 (635597)	196270 (47595–464190)	MRC, 7.6 (44.0)
Diagnostics	41	25173418	4.2%	613 985 (1 797 939)	82787 (14835–410458)	MRC, 4.3 (17.3)
Antimicrobial resistance	33	20773195	3.5%	629490 (1775416)	125119 (59327–236201)	European Commission, 8.9 (42.7)
Primary care	19	4452155	0.7%	234323 (401638)	49368 (11333–282707)	Wellcome, 2.7 (61.5)
Economics	7	1143190	0.2%	163 312 (134 121)	82872 (70853–234309)	Wellcome, 0.4 (30.7)
Behavioural science	20	3849174	0.6%	192458 (122607)	195533 (109439–308732)	MRC, 2.8 (72.2)
Non-HIV sexually-tra	ansmitte	ed infections:				
Global health	38	27186347	17.5%	715430 (1184356)	289717 (70843–737257)	DFID, 12.5 (46.1)
Vaccinology	14	3537045	2.3%	252646 (325470)	116207 (62976–237470)	Department of Health, 1.2 (34.6)
Therapeutics	11	3793661	2.4%	344 878 (331 566)	242343 (144138–320031)	Charity, 2.1 (54.5)
Paediatrics	12	1217304	0.8%	101 442 (204 546)	31972 (14098-80664)	MRC, 0.7 (60.6)
Diagnostics	123	44705952	28.7%	363463 (931522)	72293 (11793–175234)	Charity, 15.5 (34.5)
Antimicrobial resistance	5	5741870	3.7%	1 1 4 8 3 7 4 (2 4 7 2 3 0 6)	6470 (776–165259)	DFID, 5.6 (97.0)
Primary care	41	4988181	3.2%	121663 (248283)	18389 (11450–172042)	Department of Health, 2.4 (48.7)
Economics	6	2573574	1.7%	428929 (550030)	201856 (131999–514066)	Department of Health, 2.3 (91.9)
Behavioural science	18	3260456	2.1%	181136 (128084)	181211 (98963–247826)	MRC, 1.8 (56.3)

SD - standard deviation; IQR - interquartile range, MRC - Medical Research Council, DFID - Department for International Development

Where data are available and presented, the global burden of disease, measured in disability adjusted years (DALYs), was correlated with levels of research investment (**Table 4**). Time periods were chosen to reflect the years in which burden data was available. From 2004 DALYs, there is an overall investment of GBP 10.20 per DALY for HIV research, and GBP 14.93 per DALY for other STIs. Furthermore, there was investment of GBP 6.53 per DALY for chlamydia research, and relatively less investment in syphilis (GBP 0.37) and gonorrhoea (GBP 0.39). Using 2010 burden data, which is the most recent time period for which complete burden data was available, the relative invest-

ments against burden are – HIV GBP 7.33, other STIs GBP 14.18, chlamydia GBP 34.29, syphilis GBP 0.11 and gonorrhoea GBP 4.92. Annual investment over time increases for HIV research, but noticeably decreases for research of other STIs (**Figure 1**).

DISCUSSION

Our study is the first systematic analysis of research funding for STI research, including STI–related HIV, awarded to UK institutions. Over the 17–year time period of the Viral hepatitis

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Disease	Number of studies	Total funding (GBP)	DALY 2004	DALY 2010	Total investment relative to 2004 burden (GBP per DALY)	Total investment relative to 2010 burden (GBP per DALY)	Annual Investment 1997–2004 (GBP)	Annual Investment 2005–2010 (GBP)	Annual investment 2011–2013 (GBP)
HIV	873	596800543	58512843	81457000	10.20	7.33	30178341	37 300 762	43856416
non–HIV STIs:	402	155630214	10424871	10978000	14.93	14.18	11322986	8005387	5671334
Chlamydia	119	24485887	3748198	714000	6.53	34.29	2182799	706665	927836
Gonorrhoea	20	1388703	3549975	282 000	0.39	4.92	96047	30004	146768
Syphilis	5	1061560	2846113	9578000	0.37	0.11	96930	47 686	0
Candida	87	29458307	n/a	n/a	n/a	n/a	1259942	2117066	2225459
Mycoplasma	3	245667	n/a	n/a	n/a	n/a	5139	34093	0
HPV	164	58254838	n/a	n/a	n/a	n/a	4489759	2723738	1998113
Herpes simplex virus	10	2 530 037	n/a	n/a	n/a	n/a	2171198	782286	1054630

n/a

Table 4. Comparisons between investment in HIV and other sexually transmitted infections (STIs) research and global burden of disease

DALY – disability-adjusted life year, HPV – human papilloma virus, n/a – not applicable

n/a

n/a

74448

study, there is consistent funding for HIV research along the entire research pipeline in all types of science, including phase I–III trials. However, this is not replicated for other STIs where much research is categorised as translational research and there are fewer preclinical studies. HIV studies are typically larger in size, and HIV received almost four times as much funding as other STIs combined. Within HIV, global health and therapeutics studies received most investment, whilst other STI studies focused on global health and diagnostics. Non–HIV STIs broadly experienced a decline in annual research investments over time, and relative to global burden, syphilis and gonorrhoea are relatively less well funded than HIV and chlamydia. Total funding per annum is unpredictable.

A global HIV research infrastructure is now well established, and this is partly so because of the formation of UN-AIDS, an over-arching well-funded independent body that has successfully encouraged investment, collaborative work and sustained political leadership [19,20]. There are other groups tracking specific aspects of global HIV research funding [21], so the research gaps may be less obvious than in other disease areas. Substantial public and philanthropic investments have been directed towards the development of an HIV vaccine, shown both within this UK analysis here and also in international projects [21]. This global quest has proven relatively fruitless so far but has potentially very high impact should the goals be achieved. Preventive measures may be the most effective approach in the long-term, and there are widespread efforts to research and develop microbicides [21] and understand how best to implement effective behaviour change [22,23]. Having closely observed the UK portfolio of HIV research, it is arguably the large scale behavioural science studies that are most lacking by comparison with the USA

and Global South, as well as how to maximise the effectiveness of genitourinary medicine clinics and other services in primary care that offer HIV testing. Research may also focus on gaining a better understanding of how to increase testing in high risk groups such as UK men who have sex with men, a key population which continues to experience HIV incidence comparable with generalised epidemics.

9306

n/a

0

0

Antimicrobial resistance (AMR) is a global threat, and has historically been under-funded in the UK [24]. There have been few new antibacterial therapeutics in recent years and there are several reasons for this, including the pharmaceutical industry perceiving a lack of return on their investment compared to long-term chronic illnesses [25] resulting in market failure [26]. The levels of resistance in Neisseria gonorrhoeae are exceptionally high [9], and the organism has long been known for its exceptional ability to evolve resistance genes. There is virtually no UK research focussing on gonococcal AMR, although clinical trials in the US are investigating the potential of Solithromycin, a 4th generation macrolide with promising results in a phase II trial [27]. This is a critical area of potential research focus for funders and policymakers to consider, particularly in light of the 2014 review of the global economics of AMR [28].

The investments into chlamydia research are relatively strong when compared with global burdens, but this infection is the most common STI in the UK [5]. The vast majority was translational in focus and very little was categorized as global health. It may be that a much larger proportion of the research was considered to address local needs, as opposed to other infections like HIV with the significant emphasis on global health. Much HPV–related research was either pre–clinical in nature or had a focus on diagnostic and screening programmes. This approach may well change now that effective vaccines have been implemented into the UK immunisation schedules – modelling the effectiveness of vaccine programmes and research into increasing uptake and future cervical screening programmes may now take priority. Syphilis research may best centre on areas such as development of a vaccine [29], how best to implement behaviour change at the preventive level and how to ensure access to treatments for those who need it. We identified only one study *for T.* vaginalis, despite its being described as the most common curable STI in the world with implications for increased HIV transmission [30].

It is important that researchers have access to a diverse group of funding institutions, to ensure broad based investments for different areas of STI research, and to increase predictability. There is evidence that where public sector investment decreases, so does private investment [31]. Thus incentives for, and collaborations with, the private sector are important for the research environment as a whole. New sources of investment would help with the focus on priority areas. Should greater investment be secured, it will need to be spent wisely on research that clearly adds to the evidence base, does not unnecessarily duplicate existing work or knowledge, and will be high impact (measuring impact will vary depending upon the type of science addressed in the research). A coordinated proactive approach between existing funders, and international co-operations where required, would help further identify and fund priority areas, and international systematic analyses similar to that reported here could be replicated to provide detailed information on the current and historical funding landscape in other countries. Future linkage between investment and outputs of research such as publications, impact on policy and products such as databases would give some indication of the power and quality of research.

Our study has several limitations, which have been highlighted and discussed in detail elsewhere [11]. There was little publicly–available data from the pharmaceutical industry. Hence, there is a data gap particularly in relation to funding of clinical trials and the development of vaccines and diagnostics, which the pharmaceutical and biotechnology industry are mostly financing (the sums of public and charitable investment in HIV-related phase I-III trials are not replicated across most other disease areas including other STIs). Beyond disease burden, other measures, such as economic burden should also be utilised when prioritising limited resources, but little information is available regarding the economic impact of STIs. We rely on the original data being complete and accurate, and are unable to take into account distribution of funds from the lead institution to collaborating partners or any annualisation of the total funding awarded, nor can we assess quantity of each award given to overheads or the impact of the introduction of full-economic costing. Also, assigning studies to categories is a subjective and imperfect process – although we used at least two researchers to do this to reduce inter-observer error. Our study focuses on UK-led investments we do not know if similar patterns (eg, a lack of public or charitably-funded clinical trials in STIs) would also emerge if the analysis were repeated for other high-income countries, and we do not know how globally representative the UK investments are against other countries portfolios. We have not here measured either the outputs or impact of funded research. The assessment against measures of burden used the most comprehensive DALY figures available, but they are only estimates and their reliability is not precisely known; there may also be definitional differences between data sets and burden data was not available for all infections.

This analysis of UK investments in STI research highlights some areas of probable research strength, particularly with global health–related studies and more generally across the HIV research pipeline. It also suggests there are clear gaps and a need for greater research into syphilis, gonorrhoea and antimicrobial resistance. Work is ongoing to produce in–depth analyses of infectious disease research investments awarded to US institutions, and this will allow comparisons with UK strengths and weaknesses and help to set benchmarks for assessing investment vs disease burden. There is a continuing need to extend beyond this to build a global funding database of all types of HIV and other STI– related research. This analysis can be of use for funders, policymakers and researchers and act as a stimulus for targeting priority areas in STI research. Acknowledgements: We thank the Infectious Disease Research Network for their contribution to this work, and acknowledge the assistance of the research and development funding agencies for provision of data. We also pay tribute to Professor Joep Lange, who was due to be an author on this paper; he tragically died aboard flight MH17 over Ukraine on 17 July 2014.

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Association between depression and diabetes amongst adults in Bangladesh: Hospital–based case–control study

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Results The mean age (±standard deviation) of the participants was 50.4 ± 11.4 years, with a male to female ratio of 43:57. The prevalence of depression was 45.2% and 19.8% among cases and controls, respectively. In the multivariate analysis, mild as well as moderate to severe depression were significantly associated with diabetes and independent of sociodemographic factors and co–morbidity (adjusted odds ratio (OR) = 2.0, 95% confidence interval (CI) = 1.4–2.9 and adjusted OR = 6.4, 95% CI = 3.4–12.3; P<0.001 for both).

Conclusion The high prevalence and strong association of depression in individuals with diabetes in Bangladesh suggests that depression should be routinely screened for patients with diabetes at the clinics and that management strategies adequate for resource–poor settings need to be developed. Further research to determine the pathophysiological role of depression in the development of diabetes is merited.

Diabetes and depression are two major non–communicable diseases which have become global epidemics and cause significant mortality and morbidity [1–3]. Worldwide, there are 382 million people with diabetes and within next two decades this number is projected to increase to 592 million with an increasing trend in the younger population [1]. The International Diabetes Federation (IDF) estimated that in 2013, diabetes caused 5.1 million deaths and cost US\$ 548 billion in health care spending [1]. Diabetes is a major global cause of premature mortality, reduced quality of life, and imposes huge social and economic impact on health care systems, households and nations as a whole [1]. The global burden of disease study predicted that by 2030, depression is set to become the leading disease with 6.3% of the overall disease burden, and diabetes will

be in 10th place with 2.3% of the overall disease burden as a percentage of the overall disability adjusted life years [4].

Diabetes and depression often present together and represent a major clinical challenge as the outcome of each condition can be worsened by the other [5]. Several studies have reported that comorbid diabetes and depression produced the greatest level of disability compared to other conditions, predicted sub–optimum outcomes, and incurred higher health care costs that increased with depression severity [6–9]. Despite high rates of comorbid depression in patients with diabetes, depression is often unrecognized and untreated in approximately two–thirds of patients in primary care settings [10].

The prevalence of both diabetes and depression are increasing in Southeast Asia [11]. Previous studies in Bangladesh have reported that the prevalence of depression among patients with diabetes was between 15.3-36% [12-15]. However, two of these studies had no control group [13-15] whereas the other two were population-based studies with relatively small numbers of incident cases of diabetes and insufficient data to examine sociodemographic and other factors potentially influencing the association of depression and diabetes [12,14]. Based on the data available, it is difficult to appreciate the true magnitude of the problem of depression among individuals with diabetes in Bangladesh as well as exclude important confounding factors. To close these knowledge gaps, we conducted a matched case-control study of individuals with and without diabetes at a large outpatient treatment facility in the Bangladeshi capital city, Dhaka. We hypothesized that persons with diabetes would have higher prevalence of depression than persons without diabetes.

METHODS

Study design, population and place

We conducted a matched case–control study among 1182 participants from January to July 2014 in the outpatient department (OPD) of the Bangladesh Institute of Health Sciences (BIHS) hospital. Detailed methods have been published elsewhere [16]. In brief, 591 consecutive patients with diabetes diagnosed by the BIHS attending physicians were recruited as cases. For each index–case, we recruited one control matched for age (±5 years), sex and area of residence from the persons accompanying other patients in the OPD waiting room. All individuals aged between 20– 60 years were eligible for the study. Inclusion criteria for cases were: diagnosis of diabetes according to WHO criteria by attending BIHS physician. We excluded participants who were pregnant, had a terminal illness such as cancer or required urgent medical attention. The BIHS is a 500–bed national–level tertiary health care covers all disciplines of medicine under a single roof having modern biomedical laboratory and research institute for diabetes affiliated with the Diabetes Association of Bangladesh and World Diabetic Federation. The OPD of BIHS hospital has one of the largest diabetes patient's turnover in Bangladesh and serves a diverse population of about 2.2 million in Dhaka city and nearby districts.

Data collection process

Data were collected by a team consisting of one project research physician, one research officer and three research assistants experienced in hospital data collection. The team was trained for 4 weeks on diabetes epidemiology, study design, study aims and objective, interview skills, research ethics, anthropometric and blood pressure measurements. The research tools and instruments were developed by the Health Economic Group of the International Diabetes Federation (IDF) and translated into Bengali as per WHO standards of translating and back–translating. The questionnaires were pre–tested in a similar setting in BIRDEM hospital OPD for 25 cases and 25 control subjects. Feedback from the field testing was used to improve the language and contents of the questionnaire and tools.

The questionnaire contained information about socio-demographic factors such as age, sex, marital status, education, occupation, income, history of depression, diabetes, family history of diabetes, smoking history, and self-reported complications (eye, hypertension, cardiovascular diseases, kidney diseases, etc). Weight, height, and hip and waist circumference were measured using standard protocol. Blood pressure was measured using digital blood pressure monitor (Omron, SEM-1, Omron Corporation, Japan). Two repeated measurements were recorded after an interval of 5 minutes, alternating right and left hands and the average of two readings was considered. Hypertension was defined as systolic blood pressure (SBP)≥140 mm Hg and/or diastolic blood pressure (DBP)≥90 mm Hg as per JNC 7 guideline. Blood tests on HbA1c were measured at the BIHS Research Laboratory.

Level of depression was measured using the Patient Health Questionnaire (PHQ–9) which consists of nine items on a 4–point Likert–type scale with scores ranging from 0–27 corresponding to the Diagnostic and Statistical Manual of Mental Disorder (DSM–IV) diagnostic criteria for major depressive disorder [17]. Depression scores of 0–4, 5–9, and ≥10 was used to classify minimal, mild and moderate to severe depression, respectively [18]. The PHQ–9 is one of the most widely used depression screening tools in primary health care and a cut–off score of ≥10 has shown to have 88% sensitivity and 88% specificity to diagnose major depression [19]. In this study we used a previously developed

Data analysis

Data were entered into a Microsoft Access database with built-in range and consistency checks and analyzed using SPSS version 20 (IBM Corporation, NY, USA). Frequencies and percentages were calculated for categorical variables and mean±SD and median (Q1-Q3) were calculated for normality distributed and non-normally distributed continuous variable. T-test, χ^2 and Mann-Whitney U tests were performed for differences between cases and controls. Univariate analysis was performed with diabetes as the dichotomous outcome variable. The category of the independent variable with the minimum level of association with diabetes was taken as reference value. Conditional logistic regression was performed to evaluate the association of depression and other independent variables with diabetes. Odds ratios (OR) are reported with their respective 95% confidence intervals (CI) and P-value. A P-value of less than 0.05 was considered significant.

RESULTS

A total of 1265 participants were approached for this study and 1240 (98%) agreed to participate. Of those, 40 individuals were not included in the study (15 controls who had a history of diabetes, 8 cases who were pregnant, 17 cases who had no medical records available at the time of data collection). Another 18 participants were excluded before data analysis due to matching problems and incomplete information. The final sample therefore consisted of 1182 participants.

Characteristics of the study participants

The study included 1182 participants with a male to female ratio of 43:57 and mean age (±standard deviation) of 50.4 ± 11.4 years. The majority of the participants were married and Muslims. About two–thirds of the participants completed secondary education or higher. About half of the participants were housewives, and one–third were service holders or businessmen. The overall median (Q1–Q3) household income was BDT 25000 (15000–60000) or US\$ 323.42 (194.05–776.20) and about two–thirds earned BDT 30000 (US\$ 388.10) or less per month (US\$ 1 = BDT 77.3, 2014). Self–reported complications generally associated with diabetes (hypertension, cardiovascular diseases (CVD) and eye problems) were significantly higher among persons with diabetes than persons without diabetes (52.8% vs 19.3%, 10% vs 3.4% and 60.1% vs 38.1% respectively). Current tobacco use was higher among persons without diabetes than persons with diabetes (P=0.04). The prevalence of hypertension measured by systolic blood pressure (SBP) and diastolic blood pressure (DBP) was higher for persons with diabetes than persons without diabetes (35.2% vs 28.1%, P=0.009). Waist circumference and waist–hip ratio was significantly higher for persons with diabetes than persons with diabetes also had a higher number of complications than persons with diabetes reported taking higher number of medication than persons without diabetes (3.67 ± 1.76 vs 1.79 ± 1.07) (**Table 1**).

Prevalence of depression

The prevalence of depressive illness was found higher among persons with diabetes (28.3%) than persons without diabetes (16.9%; P<0.001). The prevalence of moderate to severe depression was 16.9% in persons with diabetes vs 2.9% in persons without diabetes (P<0.001) (**Table 1** and **Figure 1**).

Association between diabetes and depression

Table 2 shows the univariate analysis of factors associated with diabetes with unadjusted OR and 95% CI. No depression or minimal and moderate to severe depression were significantly associated with diabetes (OR = 2.7, 95% CI = 2.0–3.8) and (OR = 9.9, 95% CI = 5.4–18.0), respectively. Other factors found to be significantly associated with diabetes were age ≥40 years, secondary and higher education (inverse association), housewife or other occupation (such as retirees, day laborers), marital status single, obesity, hypertension and having higher number of complications (**Table 2**).

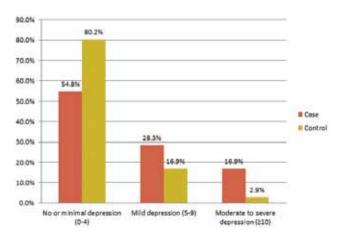


Figure 1. Prevalence of depression among study participants using PHQ–9.

Table 1. Characteristics of study participants

Variables	Case N = 591		Cont		Total n = 1182		P -value
	n N =	591 %	$\mathbb{N} = \{$	91 %	n N =	118 <u>2</u> %	_
Age (years):	11	70	11	70	11	70	
Mean±SD	51.4±11.6		49.5±11.1		50.4±11.4		0.004
<40	96	16.2	115	19.5	211	17.9	0.027
40–49	142	24.0	144	24.4	286	24.2	0.027
50–59	194	32.8	215	36.4	409	34.6	0.027
≥60	159	26.9	117	19.8	276	23.4	0.027
Sex	199	20.9	117	19.0	210	23.1	0.021
Male	255	43.1	255	43.1	510	43.1	1.0
Female	336	56.9	336	56.9	672	56.9	1.0
Marital status:	550	50.9	550	50.9	072	50.9	1.0
Married	476	80.5	517	87.5	993	84.0	0.001
			74				
Single Education:	115	19.5	/4	12.5	189	16.0	0.001
	116	10.6	76	12.0	102	16.2	0.001
No education	116	19.6	76	12.9	192	16.2	0.001
Primary	103	17.4	96	16.2	199	16.8	0.001
Secondary	190	32.1	178	30.1	368	31.1	0.001
Higher secondary and above	182	30.8	241	40.8	423	35.8	0.001
Household monthly income (BDT):							
Median (in thousands) (Q 1–3)	25 (15–42)		25 (16–40)		25 (15–60)		0.714
≤BDT 30 000	338	63.7	353	63.8	691	63.7	0.951
>BDT 30 000	193	36.3	200	36.2	393	36.3	0.951
Occupation:							
Unemployed	6	1.0	9	1.5	15	1.3	< 0.00
Service	170	28.8	248	42.0	418	35.4	< 0.00
Housewife	309	52.3	271	45.9	580	49.1	< 0.00
Others (retired, labors, etc)	106	17.9	63	10.7	196	14.3	< 0.00
Self–reported complications:							
Hypertension	312	52.8	114	19.3	426	36.0	< 0.00
Cardiovascular diseases (CVD)	59	10	20	3.4	79	6.7	< 0.00
Eye problems	355	60.1	225	38.1	580	49.1	< 0.00
Tobacco use:							
Never	471	79.7	445	75.3	916	77.5	0.040
Former (stopped 6 months)	6	1.0	2	0.3	8	0.7	0.040
Current (in last 6 months)	114	19.3	144	24.4	258	21.8	0.040
Depression (PHQ-9):							
No or minimal depression (0–4)	324	54.8	474	80.2	798	67.5	< 0.00
Mild depression (5–9)	167	28.3	100	16.9	267	22.6	< 0.00
Moderate to severe depression (≥ 10)	100	16.9	17	2.9	117	9.9	<0.00
Hypertension (SBP>140 /or DBP>90):	208	35.2	166	28.1	374	31.6	0.009
Body Mass Index (BMI):	200	JJ.L	100	20.1	511	51.0	0.009
Underweight (<18.5 kg/m ²)	9	1.5	18	3.1	27	2.3	0.071
Normal (18.5 -24.9 kg/m^2)	219	37.1	235	39.9	454	38.5	0.071
Overweight $(25-29 \text{ kg/m}^2)$	274	46.4	235	46.0	545	46.2	0.071
Overweight ($\geq 3-29$ kg/m ⁻) Obese (≥ 30 kg/m ²)	88	14.9	65	11	153	13.0	0.071
	00	14.9	00	11	201	13.0	0.071
Waist circumference (WC):	1 = 4	76-1	D15	26 1	260	21.2	-0.00
Normal ($\leq 90 \text{ cm M}; \leq 80 \text{ cm F}$)	154	26.1	215	36.4	369	31.2	<0.00
High (>90 cm M, >80 cm F)	437	73.9	376	63.6	813	68.8	<0.00
Waist-to-hip ratio (WHR):		4.0		0.0	0.4		0.000
Normal (<0.90 M, <0.80 F)	29	4.9	55	9.3	84	7.1	0.003
High (≥0.90 M, ≥0.80 F)	562	95.1	536	90.7	1098	92.9	0.003
Number of complications:							
No complication	91	15.4	240	40.6	331	28.0	<0.00
1–3	451	76.3	328	55.5	779	65.9	<0.00
>3	49	8.3	23	3.9	72	6.1	<0.00
Median (IQR)	2 (2)		2 (2)		2 (2)		<0.00
Number of medications:							
1–2	157	27.2	98	80.3	255	36.4	<0.00
3–4	259	44.8	21	17.2	280	40.0	<0.00
>4	162	28.0	3	2.5	165	23.6	< 0.00

SD – standard deviation, IQR – interquartile range, Q – quartile, BDT – Bangladeshi Taka, PHQ – Patient Health Questionnaire, SBP – systolic blood pressure, DBP – diastolic blood pressure, M – male, F – female, BMI – body mass index (kg/m2)

Variables	Odds ratio (OR)	Confidence interval	P value
Depression:			
Minimal depression (0-4)	Ref		
Mild depression (5–9)	2.7	2.0-3.8	< 0.001
Moderate to severe depression (≥ 10)	9.9	5.4–18.0	< 0.001
Education:			
No education	Ref		
Primary	0.7	0.5-1.1	0.093
Secondary	0.7	0.5-1.0	0.034
Higher secondary and above	0.5	0.3–0.7	< 0.001
Age:			
<40	Ref		
≥40	4.2	1.7-10.2	0.002
Household monthly income (BDT):			
≤BDT 30 000	Ref		
>BDT 30 000	1.0	0.8–1.3	0.842
Occupation:			
Unemployed	Ref		
Service	1.1	0.4–3.2	0.876
Housewife	3.1	1.0-9.6	0.048
Others (retired, labors, etc)	3.2	1.0-9.7	0.046
Marital status:			
Married	Ref		
Single	1.7	1.2-2.4	0.001
BMI:			
Underweight (<18.5 kg/m ²)	0.5	0.2-1.2	0.098
Normal (18.5–24.9 kg/m ²)	Ref		
Overweight (25–29.9 kg/m²)	1.1	0.9-1.4	0.435
Obese (≥30 kg/m²)	1.5	1.0-2.1	0.044
Hypertension:			
Absent	Ref		
Present	1.4	1.1-1.8	0.009
Number of complications:			
No complication	Ref		
1–3	4.0	2.9–5.6	< 0.001
>3	6.7	3.7-12.0	< 0.001

Table 3. Conditional logistic regression analyses for factors associated with diabetes

Depression: Ref No or minimal depression (≥-9) 2.0 1.4-2.9 <0.001 Moderate to severe depression (≥10) 6.4 3.4-12.3 <0.001 Age (years): <40 Ref ≥40 1.71 0.65-4.47 0.278 Education: No education Ref Primary 0.76 0.46-1.24 0.27 Secondary 0.76 0.48-1.19 0.22 Higher secondary and above 0.52 0.33-0.83 0.01 Occupation: Unemployed Ref Service or business 1.70 0.49-5.83 0.4 Housewife 3.67 0.98-13.75 0.05 Others 4.92 1.345-18.00 0.02 Married Ref <th>Variables</th> <th>Odds ratio (OR)</th> <th>Confidence interval</th> <th>P-value</th>	Variables	Odds ratio (OR)	Confidence interval	P- value
Mild depression (5–9)2.01.4–2.9<0.001Moderate to severe depression (≥10)6.43.4–12.3<0.001	Depression:			
Moderate to severe depression (≥10) 6.4 3.4–12.3 <0.001 Age (years): <40	No or minimal depression (0–4)	Ref		
Age (years):<40	Mild depression (5–9)	2.0	1.4-2.9	< 0.001
<40Ref≥401.710.65–4.470.278Education:No educationRefPrimary0.760.46–1.240.27Secondary0.760.48–1.190.22Higher secondary and above0.520.33–0.830.01Occupation:UnemployedRefService or business1.700.49–5.830.4Housewife3.670.98–13.750.05Others4.921.345–18.000.02Martial status:Normal (18.5KefSingle1.501.00–2.260.05BMI:UVVUnderweight (<18.5 kg/m²)	Moderate to severe depression (≥ 10)	6.4	3.4–12.3	< 0.001
≥401.710.65–4.470.278Education: $$$$ No educationRefPrimary0.760.46–1.240.27Secondary0.760.48–1.190.22Higher secondary and above0.520.33–0.830.01Occupation:UnemployedRefService or business1.700.49–5.830.4Housewife3.670.98–13.750.05Others4.921.345–18.000.02Martial status: $$$$ $$$$ $$$$ MarriedRef $$$$ $$$$ Single1.501.00–2.260.05BMI: $$$$ $$$$ $$$$ Underweight (<18.5 kg/m²)	Age (years):			
Hore and the second set of the set of th	<40	Ref		
No education Ref Primary 0.76 0.46–1.24 0.27 Secondary 0.76 0.48–1.19 0.22 Higher secondary and above 0.52 0.33–0.83 0.01 Occupation: Unemployed Ref Service or business 1.70 0.49–5.83 0.4 Housewife 3.67 0.98–13.75 0.05 Others 4.92 1.345–18.00 0.02 Marital status:	≥40	1.71	0.65-4.47	0.278
Primary0.760.46–1.240.27Secondary0.760.48–1.190.22Higher secondary and above0.520.33–0.830.01Occupation:UnemployedRefService or business1.700.49–5.830.4Housewife3.670.98–13.750.05Others4.921.345–18.000.02Marital status:NarriedRefSingle1.501.00–2.260.05BMI:Underweight (<18.5 kg/m²)	Education:			
Secondary 0.76 $0.48-1.19$ 0.22 Higher secondary and above 0.52 $0.33-0.83$ 0.01 Occupation:UnemployedRefService or business 1.70 $0.49-5.83$ 0.4 Housewife 3.67 $0.98-13.75$ 0.05 Others 4.92 $1.345-18.00$ 0.02 Martial status: V V V MarriedRef V Single 1.50 $1.00-2.26$ 0.05 BMI: V V V Underweight (<18.5 kg/m²)	No education	Ref		
Higher secondary and above 0.52 $0.33-0.83$ 0.01 Occupation:UnemployedRefService or business 1.70 $0.49-5.83$ 0.4 Housewife 3.67 $0.98-13.75$ 0.05 Others 4.92 $1.345-18.00$ 0.02 Martial status:	Primary	0.76	0.46-1.24	0.27
Occupation: Unemployed Ref Service or business 1.70 0.49–5.83 0.4 Housewife 3.67 0.98–13.75 0.05 Others 4.92 1.345–18.00 0.02 Marital status:	Secondary	0.76	0.48-1.19	0.22
UnemployedRefService or business 1.70 $0.49-5.83$ 0.4 Housewife 3.67 $0.98-13.75$ 0.05 Others 4.92 $1.345-18.00$ 0.02 Martial status:KefSingle 1.50 $1.00-2.26$ 0.05 BMI:Vunderweight (<18.5 kg/m²) 0.32 $0.11-0.96$ 0.04 Normal (18.5-24.9 kg/m²)RefVerweight (25 -29.9 kg/m²) 1.14 $0.83-1.55$ 0.42 Obese (≥ 30 kg/m²) 1.36 $0.85-2.17$ 0.2 Hypertension:AbsentRefVersent 1.24 $0.91-1.68$ 0.17 Number of complications: 1.24 $0.91-1.68$ 0.17	Higher secondary and above	0.52	0.33–0.83	0.01
Service or business 1.70 $0.49-5.83$ 0.4 Housewife 3.67 $0.98-13.75$ 0.05 Others 4.92 $1.345-18.00$ 0.02 Marital status: $Marital status:$ $Marital status:$ MarriedRefSingle 1.50 $1.00-2.26$ 0.05 BMI: $Married (18.5 kg/m^2)$ 0.32 $0.11-0.96$ 0.04 Normal (18.5-24.9 kg/m²)Ref $Married (18.5 kg/m²)$ 0.42 Overweight ($25 - 29.9 kg/m²$) 1.14 $0.83-1.55$ 0.42 Obese ($\geq 30 kg/m²$) 1.36 $0.85-2.17$ 0.2 Hypertension: Ref $Marriension:$ Ref Present 1.24 $0.91-1.68$ 0.17 Number of complications: $Marriension:$ $Marriension:$ $Marriension:$	Occupation:			
Housewife 3.67 $0.98-13.75$ 0.05 Others 4.92 $1.345-18.00$ 0.02 Marital status: $I.345-18.00$ 0.02 MarriedRef $I.50$ $1.00-2.26$ 0.05 BMI: $I.50$ $1.00-2.26$ 0.04 Underweight (<18.5 kg/m ²) 0.32 $0.11-0.96$ 0.04 Normal (18.5-24.9 kg/m ²)Ref $I.14$ $0.83-1.55$ 0.42 Overweight (25 -29.9 kg/m ²) 1.14 $0.83-1.55$ 0.42 Obese (≥30 kg/m ²) 1.36 $0.85-2.17$ 0.2 Hypertension: $I.24$ $0.91-1.68$ 0.17 Number of complications: $I.24$ $I.24$ $I.24$	Unemployed	Ref		
Others 4.92 $1.345-18.00$ 0.02 Marital status:RefMarriedRefSingle 1.50 $1.00-2.26$ 0.05 BMI:Underweight (< 18.5 kg/m^2) 0.32 $0.11-0.96$ 0.04 Normal ($18.5-24.9 \text{ kg/m^2}$)RefOverweight ($25 - 29.9 \text{ kg/m^2}$) 1.14 $0.83-1.55$ 0.42 Obese ($\geq 30 \text{ kg/m^2}$) 1.36 $0.85-2.17$ 0.2 Hypertension:RefPresent 1.24 $0.91-1.68$ 0.17 Number of complications:Underweight ($25 - 29.9 \text{ kg/m^2}$) 1.24 $0.91-1.68$ 0.17	Service or business	1.70	0.49–5.83	0.4
Marital status: Married Ref Single 1.50 1.00–2.26 0.05 BMI:	Housewife	3.67	0.98–13.75	0.05
Married Ref Single 1.50 1.00-2.26 0.05 BMI: Underweight (<18.5 kg/m²)	Others	4.92	1.345-18.00	0.02
Single 1.50 $1.00-2.26$ 0.05 BMI:Underweight (<18.5 kg/m²)	Marital status:			
BMI: Underweight (<18.5 kg/m ²) 0.32 0.11–0.96 0.04 Normal (18.5–24.9 kg/m ²) Ref Overweight (25 –29.9 kg/m ²) 1.14 0.83–1.55 0.42 Obese (\geq 30 kg/m ²) 1.36 0.85–2.17 0.2 Hypertension: Absent Ref Present 1.24 0.91–1.68 0.17 Number of complications:	Married	Ref		
Underweight (<18.5 kg/m²)	Single	1.50	1.00-2.26	0.05
Normal (18.5–24.9 kg/m²) Ref Overweight (25 –29.9 kg/m²) 1.14 0.83–1.55 0.42 Obese (≥30 kg/m²) 1.36 0.85–2.17 0.2 Hypertension:	BMI:			
Overweight (25 -29.9 kg/m²) 1.14 0.83-1.55 0.42 Obese (≥30 kg/m²) 1.36 0.85-2.17 0.2 Hypertension: Ref 1.24 0.91-1.68 0.17 Number of complications: U U U U	Underweight (<18.5 kg/m ²)	0.32	0.11-0.96	0.04
Obese (≥30 kg/m²) 1.36 0.85–2.17 0.2 Hypertension: Ref 0.17 0.17 Present 1.24 0.91–1.68 0.17 Number of complications: 0.017 0.017	Normal (18.5–24.9 kg/m ²)	Ref		
Hypertension: Absent Ref Present 1.24 0.91–1.68 0.17 Number of complications:	Overweight (25 –29.9 kg/m ²)	1.14	0.83–1.55	0.42
Absent Ref Present 1.24 0.91–1.68 0.17 Number of complications: 0.00000000000000000000000000000000000	Obese (≥30 kg/m²)	1.36	0.85-2.17	0.2
Present 1.24 0.91–1.68 0.17 Number of complications: Image: Complex of the second sec	Hypertension:			
Number of complications:	Absent	Ref		
	Present	1.24	0.91–1.68	0.17
Na complication Pof	Number of complications:			
No complication Rel	No complication	Ref		
1-3 3.07 2.15-4.38 <0.001	1–3	3.07	2.15-4.38	< 0.001
>3 3.06 1.52-6.17 0.002	>3	3.06	1.52-6.17	0.002

BMI – body mass index (kg/m²)

Table 3 presents the results of conditional logistic regression analyses for factors associated with diabetes after adjusting for confounders. No depression or minimal and moderate to severe depression were significantly associated with diabetes (OR=2.0, 95% CI=1.4–2.9) and (OR=6.4, 95% CI=3.4–12.3) respectively. Having 1–3 complications (OR=3.1, 95% CI=2.2–4.4), ≥3 complications (OR=3.1, 95% CI=1.5–6.2), other occupations (OR=4.9, 95% CI=1.3–18.0) and completing higher secondary education and above (OR=0.52, 95% CI=0.3–0.8) were also significantly associated with diabetes, controlling for other confounding variables.

DISCUSSION

This study, to the best of our knowledge, is the first matched case–control study determining the prevalence of depres-

BMI – body mass index (kg/m²)

sion among people with and without diabetes in Bangladesh that also measures the association between depression and diabetes. Our study showed that depression, particularly in a moderate to severe form, is much more common among those with diabetes than those without the disease. In addition, we found that the association of depression and diabetes is independent of socio–demographic factors and diabetes–associated complications.

Several longitudinal studies have reported that increased depressive symptoms at baseline are associated with incident type 2 diabetes [7,20,21]. Several factors associated with depression, such as physical inactivity, hypercaloric diet, neuroendocrine and inflammatory responses resulting in increased cortisol, catecholamines, and cytokines can induce insulin resistance leading to the development of diabetes [7]. A meta–analysis showed that the risk of de-

veloping type 2 diabetes was 37% higher in depressed adults than in non-depressed adults [22].

Conversely, the psychosocial demands of diabetes management, lifestyle change, incidence of complications and resulting functional impairment may influence depression severity, decrease quality of life, and contribute to prolonged or recurrent episodes of depression [23]. Depression in patients with chronic illness might cause nonspecific amplification of physical symptoms associated with the medical condition [24]. Compared to non–depressed patients, patients with major depressive disorders were 2 to 5 times more likely to report the presence of 10 diabetic symptoms after controlling for a number of diabetes complications [25]. These results are in line with our findings of an increased number of complications associated with diabetes which might lead to or aggravate depression.

Depressive symptoms are associated with decreased glycemic control and increased diabetic complications, which worsen depression and lessen response to antidepressant treatment [26]. Previous studies have shown that the correlation between depression and poor diabetic self–care is consistent across diverse socioeconomic and cultural groups [27,28]. Comorbid depression in patients with diabetes is also associated with increased numbers and severity of diabetic symptoms and complications [29,30]. A meta–analysis demonstrated a clinically significant relation between depression and several diabetic complications had 3 times the odds to be significantly associated with diabetes.

Previous studies have shown that type 2 diabetes is associated with an increased risk of depressive symptoms [32,33]. A Bangladeshi study reported 31.6% of comorbid depression among patients with type 2 diabetes while the prevalence of depression in persons without diabetes was 12.6%, which is similar to our findings [14]. Another study in Bangladesh reported 36.2% of participants with moderate to severe depression, which was significantly higher among females [34]. A worldwide survey by WHO reported that 9.3% of patients with diabetes also had depression [6]. A meta-analysis reported that people with type 2 diabetes have a 24% increased risk of incident depression compared with people without diabetes [35]. A study in China reported that depression was three times higher among persons with diabetes compared to those without diabetes [36]. Our results show a much higher prevalence of depressive symptoms among patients with diabetes compared to previous studies in Bangladesh, which might be due to selection of samples from a specialized hospital as well as the use of different scale and cut-off values to measure depression. Also, participants with moderate to severe depression in our study had 6.4 times higher odds of having diabetes, which is almost double what is reported by a study from China [36].

A recent systematic review reported that the prevalence of depression among individuals with diabetes is higher in population with low socioeconomic status in low-andmiddle-income countries. However, the available evidence base was small [10]. We found that the association of diabetes and depression was independent of an individual's education and household income in our sample. Additionally, it was not affected by other socio-demographic factors, BMI, hypertension, or the number of diabetes-associated complications.

Even in well–funded health care systems, depression is under diagnosed and undertreated in individuals with diabetes [5]. In Bangladesh, where there is a shortage of trained workforce in mental health and diabetes, patients with comorbid diabetes and depression are even less likely to receive adequate management for both conditions [37]. This may contribute to the fact that diabetes management in Bangladesh is suboptimal even in the best clinical settings, and the majority of the patients present with high rates of complications [38].

Strengths and limitations

The strength of this study is the matched case-control design which controlled for the age, sex and area of residence of the study participants during the recruitment stage. Both case and controls were recruited at the same time, under similar conditions, by the same research assistants and from the same source population reducing confounding bias. The limitations of this study include that controls were selected on the basis of self-reported absence of diabetes, which could not be verified by laboratory investigations. However, our study physician ensured that the controls were not on any anti-diabetic medications. We used PHQ-9 which was not designed to measure clinical depression. However, PHQ-9 is an efficient and valid tool and has been commonly used to identify depression in primary health care in previous studies [13,39]. Furthermore, we measured depression at a single-time point and did not consider the use of antidepressants, which might have misclassified our participants. Finally, our data on complications are self-reported by participants for cardiovascular diseases, eye problems and kidney diseases which could not be verified by clinical or laboratory investigations. They were however verified to the extent possible by a review of the participants' medical records. Well-designed longitudinal studies with objective measurements of clinical complications and measures of neuroendocrine markers will help to establish the direction of association and pathophysiology of both depression and diabetes among the Bangladeshi population.

CONCLUSION

The prevalence of depression, particularly moderate to severe, is very high among adult Bangladeshis with diabetes. Therefore, patients with diabetes should be routinely screened for depression in Bangladesh and probably similar other developing countries. Management strategies and guidelines adequate for the country level need to be developed and further research to determine the pathophysiological role of depression in the development of diabetes in Southeast Asians is merited.

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Ethics approval: The objectives and importance of the research were explained to all participants prior to recruitment. Participation in the study was voluntary. The confidentiality of the participants was maintained, and written informed consent was obtained from all participants. The study was approved by the Research Review Committee and Ethical Review Committee of the International Center for Diarrhoeal Diseases Research, Bangladesh (PR–13062) and obtained an ethical clearance waiver from Ludwig–Maximilians Universität (LMU) and BIHS.

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Authorship declaration: SI, the principal investigator, is involved in concept, design, developing the intervention and the instruments, as well as in the implementation, analysis and reporting aspects of the study. LN and AL were involved in all aspects of the study and provided expert advice for the study design and writing of manuscript. UF and JS were involved in study design and reviewing the protocol. All authors have read and approved the final version of the manuscript.

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). None of the participating authors has a conflicting financial or other interest related to the work detailed in this manuscript.

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Systematic review of the global epidemiology, clinical and laboratory profile of enteric fever

© ()

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Zulfiqar A Bhutta Center of Excellence in Women and Child Health Aga Khan University Stadium Road, PO Box 3500 Karachi 74800 Pakistan zulfiqar.bhutta@aku.edu **Background** Children suffer the highest burden of enteric fever among populations in South Asian countries. The clinical features are non–specific, vary in populations, and are often difficult to distinguish clinically from other febrile illnesses, leading to delayed or inappropriate diagnosis and treatment. We undertook a systematic review to assess the clinical profile and laboratory features of enteric fever across age groups, economic regions, level of care and antibiotic susceptibility patterns.

Methods We searched PubMed (January 1964–December 2013) for studies describing clinical features in defined cohorts of patients over varying time periods. Studies with all culture–confirmed cases or those with at least 50% culture–confirmed cases were included. 242 reports were screened out of 4398 relevant articles and 180 reports were included for final review.

Results 96% of studies were from an urban location, 96% were hospital–based studies, with 41% of studies were from South Asia. Common clinical features in hospitalized children include high–grade fever, coated tongue, anaemia, nausea/vomiting, diarrhea, constipation, hepatomegaly, splenomegaly neutrophilia, abdominal distension and GI bleeding. In adults' nausea/vomiting, thrombocytopenia and GI perforation predominate. The case–fatality rate in children under 5 years is higher than school aged children and adolescents, and is highest in Sub Saharan Africa and North Africa/Middle East regions. Multi–drug resistant enteric fever has higher rates of complications than drug sensitive enteric fever, but case fatality rates were comparable in both.

Conclusions Our findings indicate variability in disease presentation in adults compared to children, in different regions and in resistant vs sensitive cases. Majority of studies are from hospitalized cases, and are not disaggregated by age. Despite higher complications in MDR enteric fever, case fatality rate is comparable to sensitive cases, with an overall hospital based CFR of 2%, which is similar to recent global estimates. This review underscores the importance of further epidemiological studies in community settings among children and adults, and the need for further preventable measures to curtail the burden of disease. Enteric fever, representing a systemic infection caused by Salmonella enteric serovar Typhi (S. typhi) and Salmonella enterica serovar Paratyphi (S. paratyphi), is a common cause of morbidity in the developing world, particularly in South and South–East Asia [1,2]. It is estimated that over 22 million cases and more than 200000 deaths of typhoid fever occurred in the year 2000, with the majority of disease burden being borne by children and adolescents in South and South-East Asia [1]. Highest incidence has been documented in impoverished, overcrowded areas with poor access to sanitation such as the urban slum areas of North Jakarta (Indonesia), Kolkata (India) and Karachi (Pakistan) with annual incidence rates of blood culture-confirmed enteric fever ranging from 180-494/100000 among 5-15 year-olds and 140-573/100000 among those 2-4 years old [3]. However, it is recognized that the assessment of disease burden from Africa remains uncertain, with recent reports suggesting that it may be an increasingly recognized but underreported problem, requiring further prevalence studies [4-6]. Prevalences ranging from 0% to 4.23% have been reported from Kenya, Africa, in a recent review [7].

Despite the high burden of disease, challenges in the diagnosis and management of enteric remain. Clinical diagnosis of enteric fever is nonspecific and mimics other febrile illnesses like malaria and dengue fever and influenza [5,6]. This is particularly true for children who can present with atypical signs and complications such as neurological dysfunction, nephropathy and cardiac abnormalities [4,8,9] and thus lead the clinician away from a diagnosis of enteric fever. Attempts have been made to develop and validate clinical algorithms [10,11], without becoming mainstream for usage in diagnosis. The lack of availability of the blood cultures, in many small hospitals and community settings in endemic populations is an additional limitation, as is the low yield of the test due to prior antibiotic treatment or sampling issues in young children [12,13]. These factors can contribute to delayed diagnosis and/or inappropriate treatment [12,14].

The emergence of drug resistance and changing patterns of both multi–drug (MDR)(resistant to all three traditional first–line agents: chloramphenicol; ampicillin; and co–trimoxazole) and fluoroquinolone resistant *S. typhi* and *S. paratyphi* [12,15] has been associated with reported changes in the severity and clinical profile of enteric fever [6,16-19].Nearly 60% of typhoid fever isolates tested in Kolkata and Karachi and 44% of those in Hue, Vietnam were resistant to nalidixic acid; making these cases less responsive to commonly used second line agents such as ciprofloxacin and other fluoroquinolones [3,14]. This has not only narrowed the therapeutic options in high disease burden countries but has also lead to increased treatment costs, severity of illness, higher rates of complications and higher case fatality rates [6,14,17,20,21].

Although enteric fever is essentially a paediatric disease in South Asia, there is dearth of retrospective and prospective studies done in children with culture proven enteric fever in the global literature [22]. Furthermore, most studies on enteric fever represent hospitalized subjects and the differences in the clinical features and severity of the disease may also differ substantially from those not requiring hospitalization. Hospitalization rates of up to 2–40% among culture–confirmed ambulatory enteric cases were found in five different study sites in Asia [23], but data from those not hospitalized could represent a different disease severity and pattern. Differences in health seeking behavior of hospitalized vs community based subjects as well as differences in access may also limit generalization of available literature on clinical patterns of enteric fever [6].

In addition, reports suggest a considerable influence of age; with some studies documenting increased morbidity and mortality in younger children [19,20,23-25] while others [26,27] report comparatively better outcomes in this age group. Reports also suggest differences in presentation and outcomes between children and adults [19,20,28].Data from individual studies suggest a difference in clinical spectrum of disease amongst geographical locations in high-income and low and middle-income countries. In a report from an Ethiopian children's hospital (1984-1995), intestinal perforation occurred in 27 patients (25%) out of which 10 (37%) died [29]. During a similar time (1982-1995) in Taiwan, only 2/71 cases of intestinal perforation were reported in children [30].Prevalence of co-morbidities such as HIV, differences in antimicrobial resistance patterns, over-the-counter antibiotic availability, substandard antibiotic preparations, lack of pipe-borne portable water supply, health system functionality and health seeking behaviors all weigh in to the differences seen in disease spectrum, complications and mortality across regions.

No comprehensive systematic review exists describing the differences in clinical features of enteric fever and the frequency of its complications by various age groups. Further, the differences in clinical presentation by economic and geographical regions and by drug resistance patterns have not been systematically investigated.

This systematic review assesses the clinical profile of enteric fever across different regions and age groups (children vs adults). We also compare the epidemiology of enteric in hospitalized and community settings and in children infected with multi–drug resistant vs sensitive strains of *S. typhi*. Finally we describe the relationship between multidrug resistance patterns and case–fatality rates over time.

METHODS

We searched PubMed for studies limited to Humans (1964 onwards; last searched December 2013), and English language using MeSH and text words as shown in **Figure 1**. We conducted additional parallel searches for the following to ensure comprehensive identification of all relevant reports: a) non–English language studies (title/abstracts screen); b) clinical trials; c) relevant articles were manually retrieved from reference lists and other pertinent studies, known to the authors and not already retrieved from PubMed were included ("author's collection").

All studies indicating documentation of clinical features, based on title and/or abstract, were retrieved in full-text where available (**Figure 1**). Regional break–up of countries was taken from the World Bank list of Economies (updated April 2012) [31].

Inclusion criteria

We included studies which reported clinical features from diagnosed cases of enteric fever. Diagnosis was based on either a positive culture (blood, bone marrow, other sterile site–stool, urine) or a positive serological diagnostic test (Widal test/Typhi Dot test), as long as the diagnosis was confirmed by culture tests in at least 50% of these cases. Outcome data in children (age as author defined, or 0–15 years) or adults (age as author defined, or 12 years and above) was included if given in disaggregated form. We included clinical trials, vaccine trials, diagnostic studies, only where any clinical features were described provided they met the pre–defined criteria (**Box 1**).

Exclusion criteria

We excluded case reports (as indexed, or those with a sample size ≤5), studies reporting mixed age groups (ie, 2 to 55 years) where disaggregation on age was not stated, with some or all cases diagnosed only on clinical suspicion and reports of selective patient groups (eg, all complicated, or all HIV cases, or all cases presenting with diarrhea). Studies using only a clinical diagnosis or serological diagnostic tests only (Widal test/Typhi Dot test), without culture confirmation were excluded. For studies reporting data for *S*.

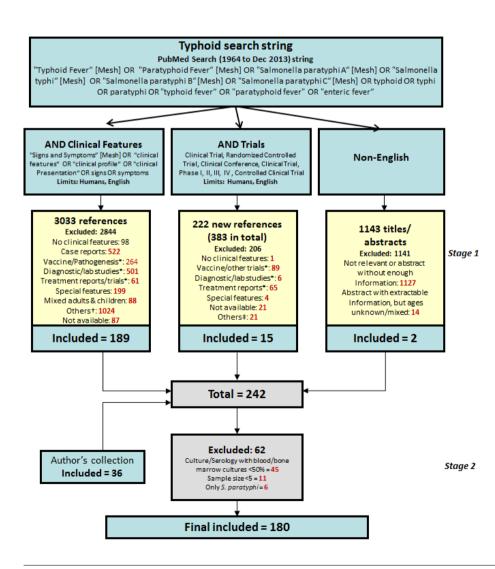


Figure 1. Search methodology. *Mixed ages, no clinical features or excluded complicated cases on enrollment. †"Others" (1024) includes: Studies on Typhoid carriers (44) Non-typhoid (mostly Rickettsia)/diarrheal diseases/other Salmonella (561) General public health/sanitation (58) Not relevant/ other laboratory-based/miscellaneous (112) Reviews, letters, editorials (249). #"Others" (n=20) includes: Non-typhoid(mostly Rickettsia)/diarrheal diseases/other Salmonella (n=1), General public health/sanitation (n = 1), Not relevant/other laboratory-based/ miscellaneous (n=14), Reviews, letters, editorials (n=5).

Box 1. Pre-set inclusion criteria

- 1. Studies must have clearly documented data on at least one clinical feature (other than drug resistance or mortality)
- 2. Studies were included from 1964 onwards as well as articles not indexed in PubMed before that at the time of searching
- 3. Number of cases reported on in each study had to be more than 5 (n ${\geq}5)$
- 4. Studies with cases of only S. typhi were included, unless data was given for both *S. typhi* and *S. paratyphi* in an aggregated form which could not be separated
- 5. Studies must include enteric fever of all severity (eg: excluded if only uncomplicated cases were included)
- 6. Studies must have at least 50% or more culture positivity (blood, bone marrow, urine or stool) along with serologically positive cases (not included if only diagnosed on clinical basis)
- 7. Cases must be in distinct age groups-children or adults
- 8. Studies must not be from a certain population subset (eg, all HIV positive, all intestinal perforations)
- 9. Studies that were not in English must have adequate, extractable information in the abstract
- 10. Studies published from the same hospital/region and during the same time period were considered as duplicate/ overlapping data and counted once using the largest reported denominator

typhi and *S. paratyphi* separately, only data for *S. typhi* were extracted; however if studies did not present data separately, data was included as both *S. typhi* and *S. paratyphi*.

In addition to baseline characteristics, geographical location, resistance and clinical features, data were also extracted separately where available for different age groups and for multi-drug resistance and sensitive isolates. Clinical features were used as author defined or as a given set of definitions if otherwise undefined (Chart 1 in **Online Supplementary Documentation**). For each clinical feature, we extracted the number of patients with the event and the number of patients assessed for the feature. Similar features were grouped together (such as "encephalopathy" and "lethargy" grouped under "altered mental status"); the largest uncombined numerator was used when several similar features were reported in a study.

Statistical methods

Data was double entered into Microsoft Access 2007 and tabulated using Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA) spreadsheets. Frequency tables of clinical features were calculated also using Microsoft Excel. Further analysis was done using χ^2 -testing for different ages (0–5 years vs 5–10 years; children 0–5 years and 5–10 years vs adults), for economical/geographical regions (Af-

rica vs South Asia); for hospital vs community settings and for MDR strains vs sensitive strains). The level of significance was set at <0.05and odds ratio (OR) are reported for likelihood of clinical feature between different categories. All analysis was done using OpenEpi [32].

RESULT

Included studies

242 reports were screened out of a total of 4398 articles retrieved with the search strategy (Stage 1). All studies with culture (blood, bone marrow, other sterile site stool, urine) confirmed enteric fever were included, as well as serologically confirmed enteric fever if percentage of culture confirmed cases was more than 50% (Stage 2). Disaggregated age data from these studies, if available, were also extracted assuming a similar proportion of culture–confirmed cases in each age group. Categorization of excluded studies is shown in **Figure 1**.

A total of 180 reports were included for final review. **Figure 2** summarizes the characteristics of included studies (153 primary references and 27 references with overlapping data): 82 studies were on children, 63 on adults and 8 studies provided disaggregated data for adults and children (2 reports from overlapping or potentially overlapping data). Urban, hospital–based, inpatient retrospective studies were predominant. Data for resistance and relapse were

Regions represented South Asia: High income countries: Sub-Saharan Africa: East Asia & Pacific: Europe & Central Asia: Middle East & North Africa: Latin America & Caribbean:	41% 23% 14% 12% 5% 2% 3%
Age groups Children Adults Data for both separated	54% 41% 5%
Study type & setting Retrospective studies Hospital-based Urban location Inpatients Study culture status Culture confirmed S. typhi data only Outcomes reported Comorbids (incl. malnutrition) Mortality reported Relapse reported MDR reported	43% 93% 96% 77% 79% 72% 33% 75% 40% 25%

Figure 2. Breakdown of included studies. 8 studies with disaggregated data for Adults and Children are counted only once in Child category, 27 studies had overlapping/duplicate data (Total 180). MD – multidrug resistance; FQ – fluoroquinolones. uncommonly presented. Studies with only *S.typhi* were 72%, while 28% had representation of both *S. typhi* and *S. paratyphi* which could not be separated out. **Figure 3** shows the geographical representation of countries with included studies with the relative contribution of data from different regions. India far outranked other countries, with 46 studies in total (41% of included studies).

Epidemiology of enteric fever in children vs adults

Studies in adults and those with data from children in disaggregated age groups were tabulated, from all available settings (Table 1 and Table S1 in Online Supplementary Document). Fever was universal (97%-100%) and a coated tongue was consistently noted in all children's age groups (71%–85% range). Signs and symptoms such as anaemia (71%), leukocytosis (47%), hepatitis (36%) and hepatomegaly (50%) were more common among preschool children (under 5 years) than in other age groups, while headache and abdominal pain/tenderness was reported to be less common in this age group (14% and 20% respectively). Altered mental status (30%), signs of URTI (22%), leucopenia (57%), abdominal pain/tenderness (70%) were common in school-aged children. Headache (75%), abdominal distension (66%), cough (60%) and pneumonia (19%) were more common in older children aged 10-17 years. In contrast, more adults presented with nausea/vomiting (49%), splenomegaly (39%), GI perforation (5%), and thrombocytopenia (52%). Relative bradycardia, chills/rigors and dehydration were also frequently reported. Toxicity throughout the ages was found to be 26–38%. GI perforation was more common as age increased. Children were infected with MDR strains in 22–25% cases, as compared to more than half of enteric cases in adults which were MDR. Relapse was similar in all ages, but pre–schoolchildren had the highest fatality rates (6%), compared to all other age groups.

In comparing children 0–5 years with children aged 5–10 years, different features were found to be more likely to occur (Table S2 in **Online Supplementary Document**), and after pooling data for children under 10 years compared to adults (author defined ages or aged 12 and above), the features more likely to occur in children are shown in and Table S3 in **Online Supplementary Document**.

Regional spectrum of enteric fever in children

Data was provided from above referenced studies on children as well as age disaggregated studies—in total 90 studies (**Table 2** and Tables S1 and S2 in **Online Supplementary Document**). In almost all regions, 40% of enteric cases presented after receiving prior antibiotics. MDR enteric fever was highest in the Middle East & North Africa from 3 studies, followed by South Asia. Fluoroquinolone resistance was reported rarely in almost all regions. The most common feature globally was fever. Other common features were anaemia (highest in South Asia), hepatomegaly (commonest in East Asia & Pacific), and coated tongue. Toxicity and relative bradycardia was seen highest in Sub Saharan Africa. Diarrhea was more common than consti-

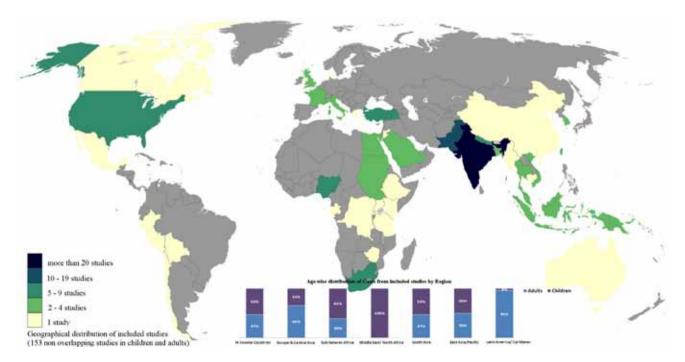


Figure 3. Map of geographical distribution of included studies.

Table 1. Epidemiology of enteric fever by age (references to studies in Online Supplementary Document)

	0–5 yi	ears (15 s	TUDIES)*	5—10 yı	ears (8 stud	nes)†	10–17	YEARS (5 STU	JDIES)‡	Adults \geq	212 YEARS (73	3 STUDIES)§
	n	Ν	%	n	N	%	n	Ν	%	n	N	%
Signs and symptoms–systemic:												
Fever	265	274	97	194	194	100	39	39	100	2287	2337	98
High grade fever	11	77	14							111	292	38
Headache	15	104	14	70	125	56	6	8	75	1149	1830	63
Toxicity	169	492	34	184	586	31	70	268	26	208	543	38
Rash or rose spots	2	12	17	6	93	6	5	84	6	75	982	8
Coated tongue	28	33	85	154	190	81	32	45	71	490	881	56
Respiratory and abdominal:												
Cough	58	187	31	78	231	34	32	53	60	595	1459	41
Nausea or vomiting	61	193	32	88	194	45	5	39	13	792	1628	49
Diarrhea	286	665	43	173	752	23	94	276	34	1118	2407	46
Constipation	52	439	12	177	752	24	31	276	11	382	1570	24
Hepatomegaly	261	526	50	276	630	44	93	245	38	555	1903	29
Splenomegaly	165	635	26	228	789	29	71	290	24	883	2278	39
Abdominal pain or tenderness	29	143	20	136	194	70	19	39	49	981	1827	54
Abdominal distention or ileus	24	131	18	90	190	47	35	53	66	139	831	17
Laboratory features:												
Anaemia (Hb <12 g/dl)	50	70	71	21	31	68				487	1687	29
Leukopenia (<5×10³/µL)	17	81	21	71	125	57				800	2248	36
Leukocytosis (>15×10³/µL)	198	417	47	91	558	16	27	237	11	32	238	13
Complications:												
Shock or hypotension	3	63	5	9	97	9	0	36	0	145	1559	9
Altered mental status	27	197	14	86	287	30	4	75	5	972	3339	29
Pneumonia or chest signs	28	194	14	57	318	18	15	81	19	205	1921	11
GI bleeding	8	158	5	11	189	6	6	75	8	177	2557	7
GI perforation	1	127	1	5	194	3	0	31	0	110	2183	5
Outcome:			-				-					
Relapse	18	399	5	29	614	5	14	273	5	66	1516	4
Death	38	656	6	10	751	1	1	75	1	197	4698	4

n-number with feature, N-number assessed

*Includes studies with data for under 1, under 2, under 3 and under 4 year-olds.

†Includes studies with data for 5 to 12, 5 to 13 and 6 to 12 year-olds.

‡Includes studies with data for 10 to 14, 10 to 15 and 10 to 17 year–olds.

\$Includes a large number of adolescents, since author definition of adults was very varied (eg: 12 years and above, 15-59 years).

pation, except in East Asia/Pacific. Sub Saharan Africa and Middle East/North Africa had a higher occurrence of abdominal distension and ileus, as well as GI perforation (6%). High income countries reported more weakness/malaise, rose spots and an intermittent pattern of fever. Relapse was consistently low: 2–9% and case–fatality rate ranged from 1–6%, highest in Sub Saharan Africa and North Africa/Middle East regions.

In comparing Africa (Sub Saharan Africa and Middle East/ North Africa) to South Asia, significant findings more likely to occur in children from African countries are presented in Table S6 in **Online Supplementary Document**.

Hospital vs community-based studies in children

Data was derived from 83 prospective or retrospective studies or treatment trials of hospitalized, predominantly inpatient children from urban areas (**Table 3** and Table S7 in Online Supplementary Document). Data meeting the predefined criteria was scarce other than from hospital based studies, and could be extracted from only 6 studies conducted in community settings or health centers (outpatient) on children. Hospitalized children (Table S8 in Online Supplementary Document) presented most commonly with highgrade fever (odds ratio (OR) 4.7, 95% confidence interval (CI) 3.5-6.4), hepatomegaly (OR 7.1, 95% CI 4.2-12.0), nausea/vomiting (OR 2.0, 95% CI 1.6-2.6), abdominal distension (OR 7.4, 95% CI 2.7-20.0), and coated tongue, anaemia and neutrophilia. Diarrhea (OR 5.2, 95% CI 3.8-7.2) and constipation (OR 4.2, 95% CI 1.9-9.6) were also associated more in hospitalized children. Other findings more likely to occur in hospitalized children were splenomegaly (OR 2.7, 95% CI 1.7-4.0); GI bleeding (OR 9.0, 95% CI 1.2-64.4); pre-treatment antibiotics received (OR 2.8, 95% CI 2.0–4.0) and duration of illness ≤1week (OR 1.8, 95% CI 1.3-2.4). Rose spots were an uncommon finding (5%). In all of the isolates reported in these studies, MDR

 Table 2. Spectrum of enteric fever by economic and geographical regions (references to studies in Online Supplementary Document)

	Нібн іл (17 st	ICOME CO UDIES)	UNTRIES		e & C e (4 stud		Sub-S# (12 stu	haran Af dies)	RICA		.e East a (3 sti		South / (41 stu				Asia & F (11 stui	
	Ν	Ν	%	n	Ν	%	n	Ν	%	n	Ν	%	Ν	Ν	%	n	Ν	%
Demographics/history:																		
Blood/bone marrow isolates	540	710	76	122	131	93	1069	1382	77	250	281	89	5280	5736	92	891	1012	88
Pre-treatment antibiotics	10	13	77	6	80	8	15	35	43				1804	3152	57	255	570	45
Duration of illness ≤1 week	68	161	42				343	574	60	92	150	61	879	2013	44	203	325	62
Multi–drug resistant isolates	10	288	3	0	72	0	0	120	0	60	60	100	1885	4214	45	150	459	33
Fluoroquinolone resistance	0	12	0	0	8	0							25	1169	2	0	326	0
Signs and symptoms-systemic:																		
Fever	614	639	96	119	123	97	920	1005	92	103	131	79	4490	4800	94	673	688	98
High grade fever	3	13	23	72	72	100	204	438	47				2085	3178	66	68	126	54
Relative bradycardia	77	271	28	2	96	2	285	573	50	12	150	8	21	482	4	40	258	16
Headache	115	481	24	64	123	52	374	909	41	73	131	56	425	3730	11	209	609	34
Toxicity	1	71	1				198	378	52	8	71	11	1072	3486	31	83	231	36
Rash or rose spots	97	523	19	6	104	6	1	792	0	9	221	4	7	960	1	38	542	7
Dehydration	31	111	28	3	24	13	66	278	24	22	71	31	3	50	6	18	167	11
Coated tongue										81	150	54	314	608	52	140	195	72
Respiratory and abdominal:																		
Cough	122	434	28	23	96	24	146	426	34	149	281	53	530	2823	19	263	786	33
Nausea or vomiting	229	582	39	16	51	31	211	535	39	33	71	46	1634	4556	36	287	684	42
Diarrhea	269	609	44	26	51	51	592	1161	51	43	131	33	1335	4503	30	308	922	33
Constipation	73	383	19	3	24	13	61	324	19	0	0		254	3895	7	240	772	31
Hepatomegaly	145	414	35	79	123	64	103	405	25	62	131	47	2060	4510	46	545	801	68
Splenomegaly	168	512	33	55	123	45	153	555	28	195	281	69	1441	4714	31	239	989	24
Abdominal pain tenderness	215	555	39	20	51	39	420	975	43	77	131	59	978	3782	26	385	786	49
Abdominal distention or ileus	20	206	10	9	51	18	236	809	29	103	221	47	254	4097	6	198	732	27
Laboratory features:																		
Anaemia (Hb <12 g/dl)	78	209	37	11	25	44	410	936	44	16	62	26	2284	3132	73	191	566	34
Leukopenia (<5×10³/µL)	84	408	21	16	49	33	89	365	24	12	69	17	204	2069	10	213	653	33
Leukocytosis (>15×10³/µL)	1	41	2	3	49	6	14	113	12	11	69	16	384	1754	22	12	177	7
Complications:																		
Shock or hypotension	2	50	4				4	131	3	4	71	6	123	2606	5	10	278	4
Altered mental status	51	417	12	44	123	36	155	1127	14				414	4928	8	191	786	24
Pneumonia or chest signs	19	305	6	1	24	4	267	993	27	66	150	44	227	1966	12	66	785	8
GI bleeding	19	548	3	2	24	8	37	1069	3	1	150	1	82	1385	6	24	616	4
GI perforation	4	449	1				63	996	6	1	150	1	13	943	1	3	274	1
Outcome:																		
Relapse	34	560	6	4	58	7	34	938	4	18	210	9	194	3614	5	7	326	2
Death	5	567	1	5	131	4	79	1328	6	10	210	5	83	4981	2	7	922	1

n-number with feature, $N-number \ assessed$

was higher in hospitalized children compared to community based studies (OR 1.7, 95% CI 1.3–2.1). The most common complications in hospitalized children was DIC (18%), followed by pneumonia, arthritis/arthralgia, altered mental status, hepatitis, and meningitis (8–15%).

MDR vs sensitive isolates in children

Thirty six studies provided either disaggregated data for MDR and drug sensitive enteric fever or had all sensitive or all MDR isolates (**Table 4** and Table S9 in **Online Supplementary Document**). Children infected with MDR isolates (sample size range from 11 to 1647) (Table S10 in **Online Supplementary Document**) presented late (duration of illness >1week) (OR 2.7, 95% CI 2.1–3.4) with pri-

or antibiotic treatment. Children infected with MDR strains were more toxic (OR 2.1, CI 1.6–2.6) and had relatively higher frequency of complications and adverse outcomes. Complications such as abdominal distention or ileus (OR 2.6, 95% CI 1.7–4.1), GI bleeding (OR 2.3, 95% CI 1.1– 4.5), shock/hypotension (OR 2.9, 95% CI 1.2–7.3); myocarditis (OR 4.2, 95% CI 1.4–12.5) and pneumonia (OR 2.2, 95% CI 1.3–3.7) were higher in cases of MDR isolates compared to pan–sensitive isolates. High grade fever (OR 0.6, 95% CI 0.5–0.8), relapse (OR 0.3, 95% CI 0.1–0.7); leucopenia (OR 0.5, 95% CI 0.3–0.8); thrombocytopenia (OR 0.1, 95% CI 0.03–0.4) and arthritis or arthralgia/myalgia (OR 0.05,95% CI 0.01–0.4) were more frequent in children with sensitive isolates (sample size range from 13 to 2531). The case fatality was 1.0% vs 1.3% in resistant and sensitive enteric respectively.

Other significant features more likely to be seen in MDR cases are shown in Table S10 in **Online Supplementary Document**.

DISCUSSION

Despite advances in public health and hygiene that have led to a disappearance of enteric fever from much of the

 Table 3. Enteric fever in children in hospital-based vs community/health-center (references to studies in Online Supplementary Document)

	Hospita studies)	L—BASED	(83	OR HE/	UNITY—I Alth Cen Patient: S)	TER
	n	Ν	%	n	Ν	%
Demographics/history:						
Blood/bone marrow isolates	7693	8786	88	407	407	100
Pre-treatment antibiotics received	2047	3709	55	43	141	30
Duration of illness ≤1week	1520	3034	50	69	193	36
Multi–drug resistant isolates	2018	4856	42	93	313	30
Fluoroquinolone resistance	11	1433	1	9	44	20
Signs and symptoms-systemic:						
Fever	6327	6787	93	394	395	100
High grade fever	2372	3622	65	60	209	29
Bradycardia or relative bradycardia	437	1830	24			
Headache	1088	5577	20	169	368	46
Toxicity	1338	4171	32	18	28	64
Rash or rose spots	158	3142	5			
Dehydration	143	701	20			
Coated tongue	535	953	56			
Respiratory and abdominal:						
Cough	1153	4588	25	62	190	33
Nausea or vomiting	2300	6038	38	95	407	23
Diarrhea	2512	6886	36	42	423	10
Constipation	625	5209	12	6	193	3
Hepatomegaly	2946	6175	48	16	141	11
Splenomegaly	2193	6937	32	25	169	15
Abdominal pain or tenderness	1901	5873	32	186	369	50
Abdominal distention or ileus	814	5889	14	4	189	2
Laboratory features:						
Anaemia (Hb <12 g/dL)	2976	4908	61			
Leukopenia (<5 × 10 ³ /µL)	602	3442	17	15	137	11
Leukocytosis (>15×10³/µL)	399	2033	20	17	136	13
Complications:						
Shock or hypotension	143	3136	5			
Altered mental status	853	7343	12			
Pneumonia or chest signs	647	4232	15			
GI bleeding	164	3603	5	1	189	1
GI perforation	84	2812	3			
Outcome:						
Relapse	291	5706	5			
Death	181	7909	2	0	209	0

n – number with feature, N – number assessed, Hb – hemoglobin, GI – gastrointestinal

developed world, it still remains the commonest bacteraemic illness in South Asian countries with children being especially susceptible [1,14]. The emergence of multi–drug resistance is very concerning due to the limited therapeutic options, high financial implications and its continuing burden in impoverished, low–income countries [6,14,21].

Several limitations should be recognized in considering our data. Our inclusion of culture proven and serological confirmed cases with culture confirmation in at least 50% of these cases may not reflect the true clinical features profile

Table 4. Demographic and clinical features of enteric fever inchildren with multi–drug resistant vs sensitive strains of *S. typhi*and *S. paratyphi* (references to studies in **Online Supplementa-**ry Document)

	Multi	DRUG RES IDIES)	ISTANT	Sensitiv studies)		
	n	Ν	%	n	Ν	%
Demographics/history:						
Multi–drug resistant isolates	1647	1647	100	0	2531	0
Chloramphenicol resistance	125	125	100	9	293	3
Fluoroquinolone resistance	0	183	0	5	55	9
Blood/bone marrow Isolates	1121	1121	100	1600	1616	99
Pre-treatment antibiotics received	10	11	91	71	335	21
Duration of illness ≤1week	151	417	36	627	1034	61
Signs and symptoms-systemic	:					
Fever	620	653	95	1350	1393	97
High grade fever	441	552	80	945	1090	87
Bradycardia or relative bradycardia	7	62	11	3	218	1
Headache	116	220	53	122	382	32
Toxicity	208	427	49	316	1006	31
Rash or rose spots	3	153	2	11	292	4
Dehydration	6	15	40	11	190	6
Coated tongue	34	77	44	8	13	62
Respiratory and abdominal:						
Cough	92	256	36	151	487	31
Nausea or vomiting	140	332	42	128	371	35
Diarrhea	201	638	32	464	1358	34
Constipation	52	487	11	137	1203	11
Hepatomegaly	456	725	63	699	1639	43
Splenomegaly	320	694	46	433	1669	26
Abdominal pain or tenderness	294	600	49	358	1259	28
Abdominal distention or ileus	55	260	21	40	434	9
Laboratory features:						
Anaemia (Hb <12 g/dL)	296	442	67	656	1170	56
Leukopenia (<5×10³/µL)	20	362	6	132	1177	11
Leukocytosis (>15 × 10 ³ / μ L)	80	300	27	231	914	25
Complications:						
Shock or hypotension	20	115	17	7	105	7
Altered mental status	80	586	14	83	638	13
Pneumonia or chest signs	32	219	15	35	484	7
GI bleeding	28	382	7	12	357	3
GI perforation	4	142	3	1	136	1
Outcome:						
Relapse	7	329	2	12	151	8
Death	23	1647	1.0	31	2339	1.3

n – number with feature, N – number assessed

of enteric fever. With the high prevalence of prior antibiotic treatment, culture proven diagnosis may have been falsely low. On the contrary, exclusion of clinically diagnosed cases may also have resulted in missing out enteric fever with atypical features. An overwhelming majority of included studies were from urban areas, with many studies from rural areas excluded for reasons such as mixed reporting of adults and children, or diagnosis solely on clinical features (Box 1). Many community level studies were also excluded due to similar reasons. Existing literature gives a varying, non-standardized representation of enteric fever since there are differences in definitions such as adult/pediatric age group cutoffs, relapse, altered mental status and other clinical features. Case series (such as "all complicated cases excluded", or "all with diarrhea") were excluded as well. Paratyphoid fever was not included to be reviewed in this systematic review as it has a different clinical spectrum, however in 28% of cases data could not be separated from typhoid fever.

Outcomes such as resistance, relapse, and mortality were not reported in all studies, leading to an incomplete representation. Confounders, such as co-morbidities, resistance, socio-economic status, heterogeneous access to health could not be adjusted for since individual level data were not analyzed. Current trends in resistance especially nalidixic acid resistance and emerging fluoroquinolone resistance have not been extensively reported. Most studies were from South Asia, especially India and Pakistan. Regions were categorized based on the World Bank list of economies, which gives geographic classifications for lowincome and middle-income economies only, while high income countries that may reflect any geographical region with an improved developmental status. Furthermore, our review is not fully representative of non–English language speaking regions of the world, although data from translated abstracts were used where possible.

Notwithstanding the above, our review highlights a number of key findings of the epidemiological pattern of enteric fever in different categories, which will assist the clinician in his diagnosis and help in the fight against enteric fever. Most of our data are from urban, hospitalized children who were more likely to have the following features: high–grade fever, nausea/vomiting, diarrhea, constipation, hepatomegaly, splenomegaly, neutrophilia, abdominal distension and GI bleeding. Young children (under 5 years) were more likely to show anaemia, diarrhea, leukocytosis, hepatitis and hepatomegaly and had a higher mortality. Older children commonly showed an altered mental status, signs of URTI leucopenia, and abdominal pain/tenderness. Adults were more likely to present with splenomegaly, GI perforation, and thrombocytopenia.

In previous literature, the commonest complications are reported to be gastrointestinal bleeding, intestinal perforation, encephalopathy and shock [5,14,33], though our review suggests that DIC, pneumonia, arthritis/arthralgia altered mental status, hepatitis, and meningitis predominate. The high frequency of DIC in our review was determined from 4 studies with one study forming the majority of the data [17]. Of note, the 'classic' stepladder temperature pattern [34] was only present in 25% of adult patients. Amongst children in the preschool years, a high case–fatality rate of 6% was found from the included studies, and death was 4.5 times more likely to occur compared to school–aged children. One included study had a particularly strong association of mortality in younger children with anaemia [17]. This high mortality and high incidence [25,35] identifies this age group as a high risk group to be addressed for vaccinations.

Other related or underlying factors influencing the clinical profile and outcomes of enteric fever are varying strain virulence, inoculum size, delays in or duration of treatment received, numerous host factors such as immune response, co–existing illnesses or infections, or underlying malnutrition [5,12,36]. These findings must be considered with caution, as our review was limited to studies with full reporting of clinical features and many studies with only outcome data were excluded. Others have recently reported increased disease severity with emergence of fluoroquinolone resistance [37].

There is insufficient and inconsistent reporting of clinical features data in MDR isolates, especially in the 1980s when the first few outbreaks were reported [5]. This may be due to a publication bias, since chloramphenicol resistance data was being reported at 10% from that time period [5]. The complications are higher with multi–drug resistant strains and these isolates have been shown to be more virulent than sensitive strains [38,39]. In this review, the case–fatality rates from all resistant and all sensitive *S. typhi* were almost the same (1.0% in MDR strains vs 1.3% in sensitive strains), reflecting a general decrease in overall mortality in treated cases since the advent of antibiotic usage and improved health care, as our review is mostly derived from inpatient reports (77% of studies).

The case fatality rate of 2% from 83 studies in hospitalized children, is comparable to case–fatality rates reviewed by Crump et al. [18] from 10 population–based studies (al-though in mixed age groups) which showed a range of 0–1.8%. However, regionally, Sub–Saharan Africa, and North Africa and Middle East had the highest case–fatality rates (5–6%). The relapse rate was low, ranging from 2–9% in all regions, reflecting improved hospital care and initiation of antibiotics, while regional differences in case–fatality rate ranged from 1–6%, highest in Sub Saharan Africa and North Africa/Middle East regions. This may reflect the higher rate of complications such as GI perforation, GI

bleed and pneumonia in these regions. As this data spans studies prior to the onset of improved health care access and surgical treatments, as well as after it reflects the overall picture of mortality enteric fever has posed on each region.

Widespread antibiotic pre-treatment was present in all regions, except Europe and Central Asia, due to prevalence of self-medication and poor health-seeking behaviors [40]. This has implications for the development of newer diagnostic tests that can replace blood culture, and ideally be more rapid, specific and cost-effective as well as sensitive. Rational use of antibiotics based on culture sensitivity patterns in different regions in imperative in curtailing the further evolution of multi-drug resistance which is already rife.

Applicability and implications for research

Although enteric fever is essentially a pediatric disease in South Asia, there is a serious dearth of data from children in community settings in global literature [3,23,25,41-43]. Hospital-based data helps show severity of infection and outcomes associated with treatment, but capturing data on clinical features from studies based in the community is imperative to strengthen our ability to pick and treat enteric fever in the most vulnerable and to better understand presentation of drug resistance and treatment outcomes of mild enteric fever. Treatment requires a low threshold for empirical antibiotics but this must be weighed against the growing rates of resistance in many regions that make treatment options complex and costly. The solution will have to be multi-faceted and include improved sanitation, vaccination implementation in high-risk populations in combination with rapid diagnosis, elimination of carriers, and rational use of the antibiotic options. Vaccinations as part of national immunizations programs (EPI) for those under

2 years of age in high risk populations will have to be the key in restriction of the spread of disease through reducing both disease transmission and new carriers, until water and sanitation are universally upgraded [33,44,45].

Future studies should be designed keeping these gaps in mind and focus on community based enteric cases. Descriptions of all clinical features, resistance patterns and mortality should be a primary objective of researchers in treatment trials, vaccine trials and prospective/retrospective studies, preferably in separate cohorts based on age (children vs adults), using standardized, clearly defined age categories. The cut–offs for MIC for fluoroquinolones have been recently revised and reports should include references of the MIC used by their laboratory. There is a need for randomized control trials for appropriate outpatient therapy in the face of rising resistance to commonly used antimicrobials.

Surveillance networks

There is a need to establish a consortium for reporting of enteric fever, especially with regard to AMR (antimicrobial resistance) as well as a central repository for genomic studies, looking at SNP related to enteric severity. The Coalition Against Typhoid [46] for example, is a global forum of health and immunization experts working to expedite and sustain evidence–based decisions at the global, regional and national levels regarding the use of enteric vaccination to prevent childhood enteric fever. They state the need to develop long and short term goals for enteric control, which include for the short term high burden and at risk populations immunizations, good hygiene practices, and for long term improvements in access to safe water and improved sanitation as their goals.

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Diarrhea is a leading cause of morbidity among children under 5 years of age globally [1]. In India, nearly 150 000 children died from diarrhea in 2010 [2]. With each Indian child under 2 years of age experiencing an average of 3.1 diarrhea episodes per year [3], the need for prompt and

Conclusion Coverage of zinc and ORS can improve with public sector programs targeted at training and increasing product availability, but demand creation may be needed to increase public sector careseeking in areas where the private sector has historically provided much of the care.

effective treatment is great. Oral Rehydration Salts (ORS) for the preven-

tion and treatment of dehydration due to diarrhea have been available

and recommended in India since the 1980s, yet the most recent nation-

al survey reports that only 26% of children with diarrhea in the past two

weeks were given ORS [4]. In India, 27% of households live below the

Results Caregivers named a public health center as an appropriate source of care for childhood diarrhea more often at endline (71.3%) compared to baseline (38.4%) but did not report increased careseeking to public sector providers for the current diarrhea episode. In logistic regression analyses, the odds of receiving zinc, with or without oral rehydration salts (ORS), increased at endline by more than 2.7 as compared to baseline. Children who were taken to the public sector for care were more likely to receive zinc (odds ratio, OR=3.93) and zinc in addition to ORS (OR=6.10) compared to children who were not taken to the public sector.

Background In Bihar, India, a new initiative to enhance diarrhea

treatment with zinc and ORS in the public sector was rolled out in

selected districts. We conducted an external evaluation to measure

changes in diarrhea careseeking and treatment in intervention dis-

Methods We conducted baseline and endline household surveys

among caregivers of children 2-59 months of age. We calculated sum-

mary statistics for household characteristics, knowledge, careseeking

and treatments given to children with a diarrhea episode in the last 14 days and built logistic regression models to compare baseline and

Public sector scale–up of zinc and ORS improves coverage in selected districts in Bihar, India

tricts.

endline values.

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poverty line and 69% live in rural areas, and thus successful diarrhea treatment programs will need to provide inexpensive or free treatment at the community level, either through community–based health workers or private sector doctors and retailers [4–6].

Zinc was added to the World Health Organization, UNI-CEF, and Indian Academy of Pediatrics' diarrhea treatment recommendations in 2004 [7–8]. Despite national guidelines, state level adoption has been slow throughout many states in India, including Bihar. As new programs begin to incorporate zinc into routine diarrhea treatment protocols in the public and private sectors, there is an opportunity to measure program success by assessing key coverage indicators and changes in careseeking behaviors. In this paper we present the results of an external, prospective evaluation of a new diarrhea treatment initiative designed to increase the quality of care among facility and community– based public sector health workers and to improve coverage of zinc and ORS among children with diarrhea in the Indian state of Bihar.

METHODS

Context of evaluation

In all15 program districts of Bihar, India (**Figure 1**), the Micronutrient Initiative (MI) led an initiative to improve diarrhea treatment quality among various cadres of public sector health care providers. MI provided training for clinic–based medical officers (MOs) and auxiliary nurse midwives (ANMs) and for community–level Accredited Social Health Activists (ASHAs) and Anganwadi Workers (AWWs). Each provider received a one-day training; the training reviewed the evidence and rationale for using zinc and ORS for diarrhea management and outlined effective strategies to counsel patients and caregivers to ensure compliance. The program also included a system of supportive supervision for the ASHAs and AWWs. To address the issue of no ORS and zinc supplies in public sector facilities, MI procured and distributed diarrhea treatment kits (DTKs), which included 14 zinc tablets and 2 ORS sachets, to public sector facilities and providers at the start of the project. The initial DTK supplies were intended to treat all cases of diarrhea among children <5 years of age for a 9-12-month period in each facility. The quantity of DTKs was estimated based on past case load. The MI kits were distributed during training and lasted until mid-2013 at which point the Bihar state government took responsibility for procuring the zinc and ORS products. The shift in product procurement and distribution was part of the original program design to ensure public sector sustainability.

The Institute for International Programs at the Johns Hopkins University Bloomberg School of Public Health and the Society for Applied Studies in New Delhi, India led the external evaluation with the objective of assessing changes in the quality and coverage of childhood diarrhea treatment in districts targeted by the public sector scale–up program (**Figure 1**). The program was focused on the public sector only, so the evaluation was heavily geared toward understanding changes in treatment behavior in that sector. We conducted two surveys among caregivers of children 2–59 months of age. A caregiver was defined as the mother or

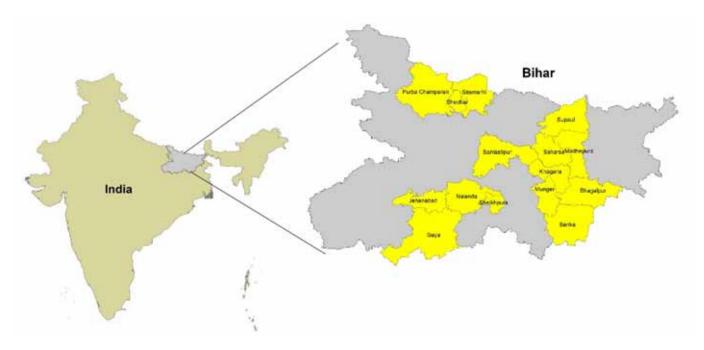


Figure 1. Districts included in the baseline and endline household coverage survey in Bihar.

primary adult providing care for the child. We conducted the baseline survey in April – May 2011, prior to the start of training and supply distribution, to determine the pre– intervention coverage of zinc and ORS for the treatment of diarrhea among children 2–59 months of age. In order to measure changes since baseline in careseeking and treatments given to a child with diarrhea in the last 14 days, we conducted an endline survey from September – December 2013 in all intervention districts.

Sample size calculation

We based sample size calculations for both the baseline and endline surveys on ORS coverage because zinc coverage was very low prior to the MI-led project in Bihar. To calculate the sample size required at baseline, we assumed baseline ORS coverage of 20.9% based on a previously published survey among children with diarrhea in the last 14 days [9]. In order to calculate the sample size required at endline, we assumed ORS coverage would increase from the 19.7% observed in the baseline survey to at least 28.5%. We increased the endline sample size to 750 caregivers of a child 2-59 months of age (ie, 50%) to ensure a sample big enough to demonstrate what is still an increase of public health importance. The sample size calculations for both surveys were conducted using STATA 12.0 statistical software (College Station, Texas, USA), with standard statistical assumptions (ie, two-sided test; alpha=5%; 80% power; and non-continuity) and were increased to account for within village clustering and a 15% anticipated refusal rate [10].

Survey procedures

All households within the selected project areas were eligible for inclusion in baseline and endline surveys. Applying seasonal two-week diarrhea prevalence to the required sample sizes, we determined that 2400 and 4995 households of children 2-59 months of age should be visited at baseline and endline, respectively. We divided the number of households equally across the 15 intervention districts because it was critical for the evaluation to have adequate representation from each of the 15 districts. For each district, we ascertained a list of villages from the 2001 census (the most recently available with village-level population data) and randomly selected villages using a population proportionate to size (PPS) sampling strategy. In each village, we limited the number of households screened for inclusion in the survey to 25 at baseline and 50 at endline. The random selection of endline villages was independent of baseline.

The survey team worked with leaders of the selected villages to divide each village into clusters of different mohallas (areas/blocks). The survey team mapped the clusters and randomly selected four from which to screen households for study inclusion. Starting at a central point within each cluster, the survey team moved from house to house using the right hand rule to identify caregivers of children 2–59 months of age until the total maximum sample per cluster was reached. For any house with more than one child 2–59 months, we selected the youngest child for inclusion in the survey. All caregivers were read a full consent document and provided a signature or a fingerprint (in the case of illiteracy) to indicate their willingness to participate in the survey. We interviewed caregivers and asked about household characteristics and typical careseeking practices for diarrhea. We then asked if the child had experienced diarrhea in the last 2 weeks and noted all careseeking and treatments for that diarrhea episode. We asked open ended questions and used pictures of zinc and ORS to aid in caregiver recall of treatments given.

All data collectors were from Bihar to ensure each could communicate with rural caregivers. Interviewer training, including classroom and field practice, was conducted in Bihar according to standard operating procedures. After each day of fieldwork, the survey forms were double checked by the supervisor and incomplete entries or logical errors were corrected by contacting the household immediately in person and by phone. This process ensured that all final forms were complete and free of logical errors prior to photocopying and data entry. Double data entry was completed by a trained data entry team in New Delhi.

We received ethical approval from the Johns Hopkins University Bloomberg School of Public Health Institutional Review Board and the Society for Applied Studies Ethics Review Committee in New Delhi, India.

Statistical analysis

We calculated means, medians and proportions for household characteristics and conducted t–tests and χ^2 tests to determine the statistical significance of differences between the baseline and endline survey populations. To compare diarrhea episode characteristics, knowledge, careseeking and treatments between baseline and endline, we built logistic regression models using generalized estimating equations (GEE) to control for within–cluster correlation (ie, village level).

We built three logistic regression models to assess the main evaluation outcome variables of zinc and ORS among children with diarrhea episode in the last 14 days. Receipt of ORS, receipt of zinc and receipt of both ORS and zinc were the dependent variables in each of the respective three models. In all models, we included round of survey (ie, baseline or endline) as the main predictor and the following variables: maternal education, sex of child age of child and careseeking. In the models of any ORS and zinc, we also included indicators of other treatment with zinc and ORS (ie, receipt of zinc was included in the regression with ORS as the dependent variable vice versa).

RESULTS

We screened 2645 and 5843 caregivers with a child 2-59 months of age in the baseline and endline, respectively (Figure 2). We asked the caregiver questions about the youngest child in this age group and found the mean age of the child to be similar in the baseline (24.5 months) and endline (24.6 months) surveys. Fifty-four percent were boys in both surveys. Two-week prevalence of diarrhea was lower at the endline survey than at baseline (16.5% at baseline vs 12.8% at endline, P < 0.05); it should be noted that the surveys were conducted at different times of year and thus change cannot be attributed to the program. The mean age of the caregiver was 26.8 (standard deviation, SD: 5.1) years at baseline and 27.3 (SD: 5.2) years at endline, and more than 60% of mothers in both surveys had never attended school. More than half of the households included in the survey possessed a below poverty line (BPL) card and more than 80% of households had no access to an improved sanitation facility (ie, toilet or latrine). Additional household characteristics are presented in Table 1.

We found that caregivers were overall better able to identify a variety of providers as sources of care for a child with diarrhea at endline (**Figure 3**). However, the largest increase in awareness was found for public sector sources. At baseline, 0.2% of caregivers named an AWW as an appropriate source of care and 1.1% named an ASHA, which rose to 10.4% and 11.9%, respectively in the endline survey. At endline we sought to understand more about the possible shift to public sector by asking each caregiver if she had ever sought care for diarrhea treatment from these community level workers; we found that 18.9% had sought care from an ASHA or AWW for childhood diarrhea. Primary health centers (PHCs) were mentioned as an appropriate source of care by 38.4% of caregivers at baseline and 71.3% at endline; private sector sources were the most widely identified in both surveys.

The main objective of the survey was to capture caregiver careseeking and treatment for the child's diarrhea episode in the last 14 days. Caregivers were more likely to have heard of ORS at endline than baseline (OR=3.07, 95% confidence interval (CI): 2.32 to 4.09) (**Table 2**). More than two–thirds of children had been taken outside the home for care for the recent diarrheal episode at the time of both surveys. The relative odds of seeking care from an ASHA or AWW were much greater at endline (OR=6.29 and 3.45, respectively). There were no differences in the proportion of children who received any treatment (82.8% at baseline vs 84.8% at endline). The odds of receiving zinc were greater at endline (OR=3.02, 95% CI 2.17 to 4.21) compared to baseline. ORS coverage also increased at endline but more modestly (OR=1.33, 95% CI 0.34 to 5.18).

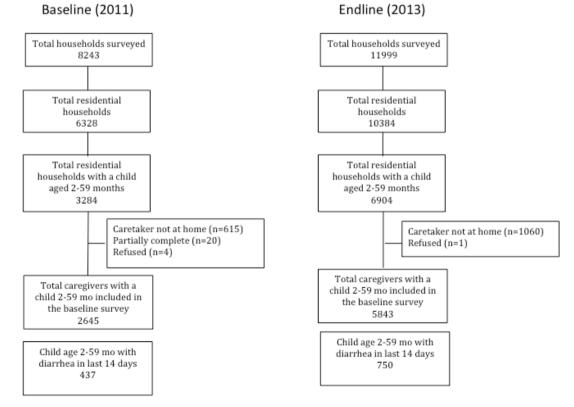


Figure 2. Survey profiles for both baseline and endline household surveys. mo – months.

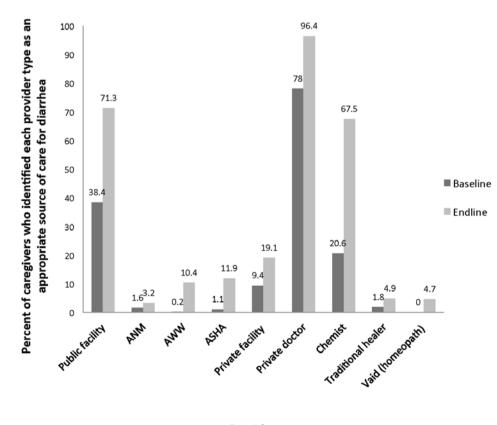
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Table 1. Caregiver and household characteristics for children 2–59 months of age with diarrhea in the last 14 days

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	Baseline n = 437 (%)	Endline N $=$ 750 (%)	P VALUE*
Mean age of child (in months)	24.5 (15.9)	24.6 (15.6)	0.916†
Caregiver characteristics			
Median years of father's schooling (range)	5 (0 to 16)	5 (0 to 15)	_
Median years of mother's schooling (range)	0 (0–15)	0 (0–17)	-
Mothers who had never been to school	292 (66.8)	477 (63.6)	0.266
Mean age of mother in years (SD)	26.8 (5.1)	27.3 (5.2)	0.940
Household characteristics			
Proportion of caregivers who purified drinking water	22 (5.0)	24 (3.2)	0.121
Proportion of households with water on premises or <30 min to source	436 (99.8)	740 (98.7)	0.885
Household toilet facilities:			
– Flush/pour flush to piped sewer system, septic tank or pit latrine with slab	76 (17.4)	100 (13.3)	0.055
– Pit latrine without slab/open pit	5 (1.1)	11 (1.5)	0.565
– No facility/open space/field	356 (81.5)	639 (85.2)	0.095
Proportion of households with BPL card	232 (53.1)	408 (54.4)	0.664
Religion of father/ head of the household:			
– Hindu	385 (88.1)	669 (89.2)	0.562
– Muslim	52 (11.9)	79 (10.5)	0.458
– Other		2 (0.3)	_
Ethnic group:			
– Scheduled caste	115 (26.3)	192 (25.6)	0.791
– Scheduled tribe	11 (2.5)	8 (1.1)	0.065
– Other backward castes	237 (54.2)	474 (63.2)	0.002
– Other	74 (16.9)	74 (16.9)	0.001

**P* values generated from χ^2 -squared analysis.

 $\dagger P$ values generated from t–test analysis.



Provider Type

Figure 3. Caregiver knowledge of appropriate sources of care for diarrhea treatment at baseline and endline.

age with a diarmea episode in last 14 days		
Characteristic	Endline vs Baseline odds ratio	95% CI*
Clinical signs and symptoms of the child's recent diarrhea episode:		
Blood in stool	0.72	0.49 to 1.06
Fever	1.20	0.93 to 1.55
Vomiting	1.01	0.79 to 1.28
hirsty	0.50	0.39 to 0.65
Lethargic or irritable	1.27	1.0 to 1.63
Sunken eyes	0.87	0.68 to 1.10
Pani ki kami (local term for dehydration)	0.87	0.68 to 1.10
Proportion of caregivers who heard/seen ORS	3.07	2.32 to 4.09
Proportion of caregivers who heard of zinc	2.14	1.58 to 2.89
Proportion of children who sought any care outside home:		
Primary health center (PHC) / government hospital / government dispensary	1.4	0.80 to 2.53
Auxiliary nurse midwife (ANM) / sub centre	6.29	0.81 to 48.92
Anganwadi worker (AWW) / Anganwadi centre (AWC)	3.45	1.01 to 11.80
Accredited social health activist (ASHA)	2.85	0.62 to 13.06
Private sector†	1.02	0.77 to 1.34
Proportion of children administered any treatment:		
Syrup, unknown	0.49	0.35 to 0.64
Tablet, unknown	0.46	0.34 to 0.62
Powder, unknown	0.03	0.01 to 0.10
Injection	0.56	0.40 to 0.78
Antibiotics	2.19	1.57 to 3.06
Antidiarrheal	3.11	2.22 to 4.35
Zinc‡	3.02	2.17 to 4.21
IV fluids	1.33	0.34 to 5.18
ORS	1.42	1.07 to 1.90

 Table 2. Characteristics of current diarrhea episode, careseeking and treatment practices among caregivers of children 2–59 months of age with a diarrhea episode in last 14 days

ORS - oral rehydration solution, IV - intravenous, CI - confidence interval

*Logistic regression analysis using generalized estimating equations (GEE) to control for village level clustering.

†Private sector includes private doctor, hospital, chemist, or traditional healer.

‡Includes caregivers who reported zinc and those who recognized zinc on picture charts.

We conducted logistic regression analyses to identify key factors contributing to zinc and/or ORS use (**Table 3**). The adjusted odds of receiving zinc, with or without ORS, increased in the endline survey by a factor of more than 2.7 as compared to baseline. Maternal education (at least 1 year of formal schooling) was also an important predictor for zinc and/or ORS use, with adjusted odds ranging from 1.46 for ORS use alone to 2.44 for combined zinc and ORS use. Children who were taken to the public sector for care were more likely to receive zinc (OR=3.93), ORS (OR=5.56) and zinc with ORS (OR=6.10) as compared to children who were not taken to the public sector. Private sector careseeking only increased the odds of receiving ORS, not zinc.

DISCUSSION

We conducted an external evaluation of an enhanced diarrhea treatment program conducted in the public sector in selected districts of Bihar, India. We found that in the 18 months between baseline and endline surveys, reported use of both zinc and ORS improved. We also observed that children taken to the public sector were more likely to receive zinc and/or ORS. This is not surprising given that the initiative was focused on training and supplies in the public sector and did not include training or procurement in the private sector. Though the private sector is currently treating the majority of childhood diarrhea cases, zinc had not been formally introduced into the private sector at the time of this program and evaluation, and there were no known private sector activities to promote zinc and ORS during the time of this public sector scale–up.

To ensure all zinc products used were captured at endline, data collectors were provided with additional training to emphasize the importance of asking caregivers for the packaging of all diarrhea treatments given to the child in addition to the picture charts provided to all data collectors for both surveys. Because zinc was not widely available at baseline, it is not likely that many of the reported unknowns at baseline were zinc. The additional training successfully led to an overall decrease in unknowns, however it also may have led to apparent increases in rates of antibiotics and antidiarrheals. The reduction in reported unknowns was greater overall than the combined increase in

Independent variables*	Zinc		ORS		ZINC AND ORS	
	OR	SE	OR	SE	OR	SE
Survey conducted at endline	2.72	0.48†	1.22	0.19	2.85	0.85†
Mother has some education	2.12	0.32†	1.46	0.22†	2.44	0.56†
Age over 1 year	1.35	0.22	0.89	0.14	1.22	0.31
Female	0.97	0.15	0.80	0.12	0.96	0.22
Public sector careseeking	3.93	0.92†	5.56	1.38†	6.10	1.73†
Private sector careseeking	1.22	0.23	4.70	1.10†	2.16	1.73†
Any zinc	_	_	1.57	0.26†	_	-
Any ORS	1.53	0.25†	_	_	_	_

OR – odds ratio, SE – standard error, ORS – oral rehydration salts

*The null values for independent variables were defined as follows: baseline survey; mother reported 0 for years of school; child <1 year of age; male; caregiver did not report any public sector careseeking; caregiver did not report any private sector careseeking; caregiver did not report zinc use in open– ended question or when probed with pictures; caregiver did not report ORS use.

†P < 0.05.

antibiotics and antidiarrheals so it is likely that much of the apparent rise in antidiarrheals and antibiotics might be the result of better identification of treatments (ie, fewer unknowns).

The evaluation was designed as a pre–post quasi–experimental design with no comparison area. This design has several limitations. Without a control group we cannot be sure all changes observed were a direct result of this initiative. However, we are unaware of any other efforts made to improve treatment quality or access to zinc and ORS in the public sector in Bihar during the period covered by these two surveys. In addition, we were not aware of any specific efforts targeting private sector zinc supplies and/or diarrhea treatment activities but did observe an increase in the number of zinc products on the market in the time between the baseline and endline surveys. It is possible that an increase in zinc available in the private sector market may have played a role in creating awareness.

We depended on caregiver recall to assess coverage of zinc and ORS for diarrhea episodes in the last 14 days and used pictures of zinc products to help caregivers recall the treatment given. Caregivers may have forgotten what treatment was given. However, if the full course of zinc was prescribed (10–14 days depending on brand), the packaging would have been available for comparison for the majority of children.

Lastly, the surveys were conducted during different seasons, which impacts diarrhea prevalence. This also could have influenced careseeking or treatments given, yet we did not see a difference in careseeking outside the home so this bias, if any, may have been minimal. Although we did not observe a significant shift in careseeking to the public sector during the course of the program, the recognition that the public sector, especially community level health workers, could be an appropriate source of care did increase. This might be considered a first step in changing careseeking behavior in the community. The public sector program was intended to improve diarrhea treatment quality and did not include demand creation activities or community level awareness activities. Therefore, the message that community health workers were now stocked with zinc and ORS for diarrhea treatment could take time to move through a community. It is possible that with time the shift will be made from awareness to careseeking. New programs might consider funding demand creation activities targeted at increasing the rate of change in the community with the hope of achieving higher community level coverage rates by increasing public sector careseeking.

With increased public sector careseeking, a renewed effort will be needed to ensure diarrhea treatment supplies are consistently in place. This initiative facilitated the availability of supplies early in the program, yet by endline only 59% of the children who sought diarrhea treatment through a public sector provider received zinc and only 50% received ORS (30% received both zinc and ORS). Lack of supplies may not be the only reason the treatments were not provided but should be considered a potential obstacle to achieving high coverage rates. If supplies are consistently problematic in the public sector, confidence in public sector care will not improve.

CONCLUSION

Diarrhea treatment is desperately in need of an overhaul in many low– and middle–income countries [11]. Zinc for the treatment of diarrhea was incorporated into international guidelines in 2004, yet coverage of zinc remains in the single digits in most countries and ORS rates have remained stagnant for decades [8,12]. Zinc and ORS for the treatment of diarrhea are simple and inexpensive. It cannot PAPERS

be assumed that high coverage rates will be achieved quickly, simply by changing a policy at the national level. In the last decade, many country–level policies have incorporated zinc, but few countries have adopted comprehensive strategies to improve diarrhea treatment [13]. Achieving high coverage does not require new technology, but it does require attention to the training needs, supply logistics, and demand creation activities in both the public and private sectors.

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Authorship declaration: CLFW conceptualized and designed the study, conducted the analysis, drafted the initial manuscript and approved the final manuscript as submitted. ST and SM conceptualized and designed the study, oversaw the field operations and data entry, contributed to the manuscript and approved the final manuscript as submitted. LML contributed to the manuscript and approved the final manuscript as submitted. REB conceptualized and designed the study, contributed to the manuscript and approved the final manuscript as submitted.

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). None of the participating authors has a conflicting financial or other interest related to the work detailed in this manuscript.

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An external evaluation of the Diarrhea Alleviation through Zinc and ORS Treatment (DAZT) program in Gujarat and Uttar Pradesh, India

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Laura Lamberti Johns Hopkins Bloomberg School of Public Health Department of International Health Baltimore MD USA Ilamber3@jhu.edu **Background** To address inadequate coverage of oral rehydration salts (ORS) and zinc supplements for the treatment of diarrhea among children under–five, the Diarrhea Alleviation through Zinc and ORS Treatment (DAZT) program was carried out from 2011–2013 in Gujarat and from 2011–2014 in Uttar Pradesh (UP), India. The program focused on improving the diarrhea treatment practices of public and private sector providers.

Methods We conducted cross–sectional household surveys in program districts at baseline and endline and constructed state–specific logistic regression models with generalized estimating equations to assess changes in ORS and zinc treatment during the program period.

Results Between baseline and endline, zinc coverage increased from 2.5% to 22.4% in Gujarat and from 3.1% to 7.0% in UP; ORS coverage increased from 15.3% to 39.6% in Gujarat but did not change in UP. In comparison to baseline, children with diarrhea in the twoweeks preceding the endline survey had higher odds of receiving zinc treatment in both Gujarat (odds ratio, OR=11.2; 95% confidence interval (CI) 6.4–19.3) and UP (OR=2.4; 95% CI 1.4–3.9), but the odds of receiving ORS only increased in Gujarat (OR=3.6; 95% CI 2.7–4.8; UP OR=0.9; 95% CI 0.7–1.2). Seeking care outside the home, especially from a public sector source, was associated with higher odds of receiving ORS and zinc.

Conclusions During the duration of the DAZT program, there were modest improvements in the treatment of diarrhea among young children. Future programs should build upon and accelerate this trend with continued investment in public and private sector provider training and supply chain sustainability, in addition to targeted caregiver demand generation activities.

Despite absolute reductions in the global number of diarrhea–attributable deaths among children under–five over the past decade, diarrhea remains a leading cause of mortality in this age group [1]. In 2013, diarrhea caused an estimated 578000 of the total 6.3 million under–five deaths [1]. In India, the number of under–five deaths attributable to diDiarrhea is also responsible for significant morbidity among children in low– and middle–income countries worldwide. There were an estimated 1.731 billion episodes of diarrhea among children under–five in 2010, approximately 98% of which were mild or moderate [2]. Repeat bouts of less severe episodes that do not progress to death can result in long–term sequelae, such as poor nutritional status, stunting and subsequent decreases in cognitive function [2-4]. In India, this risk is substantial with children aged 0–5, 6–11, 12–23 and 24–59 months experiencing an average of 2.5, 3.8, 3.1 and 2.0 diarrheal episodes per year, respectively [5].

The diarrhea treatment guidelines supported by the Government of India and the Indian Academy of Pediatrics are in accordance with the WHO/UNICEF guidelines that include reduced osmolarity oral rehydration salts (ORS) and 14 days of zinc supplementation (20 mg of zinc/d for children ≥6 months and 10 mg of zinc/d for children 2–5 months of age) [6,7]. However, despite national recommendations, the most recent National Family Health Survey (NFHS) reported ORS coverage of 26% and zinc coverage of less than 1% [8]. Focused scale–up efforts are therefore warranted but have been slow to roll–out in many states. In response to this need, the Bill and Melinda Gates Foundation funded the Diarrhea Alleviation through Zinc and ORS Treatment (DAZT) program in Gujarat from 2011–2013 and in Uttar Pradesh (UP) from 2011–2014.

The main objective of the DAZT program was to scale-up adequate treatment of diarrhea among children under-five

through public and private sector channels in selected districts. Micronutrient Initiative (MI) and FHI360 were tasked with carrying out project activities in the public and private sectors, respectively. The Johns Hopkins Bloomberg School of Public Health Institute for International Programs (JHSPH IIP) and in–country partner, the Society for Applied Studies (SAS), were responsible for conducting a large–scale external effectiveness evaluation to assess changes in diarrhea careseeking and ORS and zinc coverage over the project period. In this paper, we present the results of household coverage surveys conducted before and after program implementation in both states as part of this effectiveness evaluation. The baseline coverage surveys were carried out in 2011 in both states and the endline surveys were conducted in 2013 in Gujarat and in 2014 in UP.

METHODS

Evaluation context: study population

Gujarat and UP are representative of the various sub–national child health and economic development contexts existent within India. Of the 29 Indian states, Gujarat has the third highest GDP per capita, whereas UP ranks 26th [9]. According to the 2011 census, Gujarat's population of 60 million is the 9th largest in India but is small in comparison to that of UP, which is the most highly populated state with over 199 million inhabitants [10]. The DAZT program was implemented in 6 districts in Gujarat (**Figure 1**) with a total population of 13.2 million and approximately 2.1 million children under–five [10]. In UP, the program was implemented in 12 districts (**Figure 1**) with total and

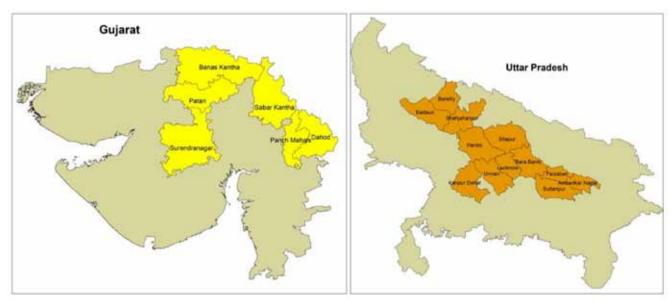


Figure 1. Map of the DAZT program districts in Gujarat and Uttar Pradesh, India. 6 program districts in Gujarat (*Banas Kantha, Dohad, Panch Mahals, Patan, Sabar Kantha Surendranagar*) and 12 program districts in UP (*Ambedkar Nagar, Bara Banki, Bareilly, Budaun, Faizabad, Hardoi, Kanpur Dehat, Lucknow, Shahjahanpur, Sitapur, Sultanpur, Unnao*). The map was generated using ArcGIS software and DIVA–GIS shapefiles [11,12].

under–five populations of approximately 41.1 million and 6.3 million, respectively [10].

In 2007, 27% of India's under–five deaths occurred in UP compared to 5% in Gujarat [13]. Although lower in Gujarat than in UP, Gujarat has the 6th highest absolute number of under–five deaths in India, outranking other states with poorer economic development and larger populations [13]. Diarrhea is a leading cause of under–five mortality in both Gujarat and UP. Prior to implementation of the DAZT program, the most recently available ORS coverage estimates of 26.3% in Gujarat and 12.5% in UP, highlighted the substantial need for focused scale–up in both states [14,15].

Evaluation context: program design

Detailed descriptions of the specific public and private sector activities of the DAZT program have been published elsewhere [16,17]. In brief, the public sector program focused on provision of training to facility–based medical officers and auxiliary nurse midwives (ANMs) and to community–level Accredited Social Health Activists (ASHAs) and Anganwadi workers (AWWs). The training sessions covered overall diarrhea prevention and management with emphasis on ORS and zinc treatment. The public sector program also addressed ORS and zinc supply shortages by securing an initial seed supply of diarrhea treatment kits (DTKs) consisting of two ORS sachets and 14 zinc tablets. These DTKs were distributed to public sector facilities in the interim period before the state and district governments assumed responsibility for supply chain management.

In the private sector, the program engaged both formally qualified doctors and informal providers. The latter cadre of informal private sector providers often lack governmentapproved degrees and/or licences and consequently operate underground; however, they provide the bulk of diarrhea treatment in many remote rural villages. In order to reach formal and informal private providers (PPs), the program implementers enlisted local non-governmental organizations (NGO) and pharmaceutical companies to visit PPs at their places of work. During these visits, the NGO and pharmaceutical representatives showed PPs videos about adequate diarrhea treatment and solicited the sale of zinc syrups and/or tablets. Representatives made repeat zinc solicitation visits to PPs; the frequency of visits was based on the provider's patient load and thus zinc-prescribing potential.

Evaluation study design

We conducted an external evaluation of the DAZT program with a prospective, quasi–experimental, pre–post design. The main evaluation activities centered on cross–sectional household surveys at baseline and endline to assess changes in diarrhea careseeking and treatment among children aged 2–59 months in intervention districts. The target population excluded infants <2 months because zinc is not advised for this age group according to the Government of India guidelines. Baseline data were collected from March– June 2011 in both states. Due to government elections that resulted in unforeseen project delays in UP, the timing of endline data collection differed by state; the endline was conducted from September–November 2013 in Gujarat and from August–October 2014 in UP.

Sample size calculations

Sample size calculations were designed to ensure adequate power to detect ORS rather than zinc coverage, since pre-DAZT zinc coverage was close to 0% in both states. For the baseline surveys, we calculated the state-specific sample sizes required for a precision estimate of ORS coverage ±7% at the alpha = 5% level, assuming coverage of 26.3% in Gujarat and 12.5% in UP as reported by the most recently conducted national survey [14,15]. At endline, we calculated the state-specific sample sizes required to detect a 10% change in ORS coverage from the level observed at baseline with 80% power at the alpha = 5% level. For both surveys, the resulting sample sizes were inflated to ensure adequate power among the two poorest wealth quintiles and to account for within-village correlation and an anticipated refusal rate of 15%. The Gujarat calculations yielded minimum sample size requirements of 375 and 398 children with diarrhea in the two-weeks preceding the survey at baseline and endline, respectively. The UP calculations yielded a minimum baseline sample size of 350 and a minimum endline sample size of 707 children with diarrhea. All sample size calculations were conducted using Stata statistical software [18,19].

Sampling design and survey procedures

For each survey, we applied two–week diarrhea prevalence to the required sample sizes in order to estimate the number of households required to achieve the necessary number of children with diarrhea in the preceding two–weeks. The respective number of households required at baseline and endline were 4200 and 5080 in Gujarat and 3889 and 7853 in UP. To ensure equal representativeness across the DAZT districts in each state, we divided the number of households evenly across the 6 districts in Gujarat and the 12 districts in UP. For each district, we employed a probability proportional to size (PPS) sampling strategy to randomly select villages on the basis of the most recently available village population census [10].

In each randomly selected village, the trained data collection team mapped and divided the area into clusters of *mahallahs* (ie, neighborhoods/blocks). The team started at a central point from within each cluster and employed the right hand rule to select households to screen for study inclusion. The screening process entailed inquiring as to whether a child aged 2–59 months resided within the household and, if so, whether the child's primary caregiver was available at the time of the visit; in multi–family households with more than one eligible caregiver, only one was selected for inclusion. The teams visited households until either a maximum of 50 caregivers of children 2–59 months of age had been enrolled or all households in the village had been visited. The team continued to visit randomly selected villages sequentially until the required number of households was met in each district.

Trained interviewers obtained informed consent from each caregiver prior to administering the survey. Interviewers read the consent document aloud and caregivers provided a signature or fingerprint (if illiterate) to indicate willingness to participate. The interviewers subsequently administered the survey to consenting caregivers. The survey included questions on household characteristics, diarrhea management knowledge and typical diarrhea careseeking and treatment practices. Extended questions on careseeking and treatment were administered to caregivers of children who had experienced a diarrheal episode in the twoweeks prior to the survey; diarrhea was defined as the passage of at least 3 loose or watery stools in a 24-hour period. If the caregiver was responsible for more than one child aged 2-59 months, she was asked to base survey responses on the youngest child in that age range.

The consent and survey procedures were conducted in Gujarati in Gujarat and in Hindi in UP. Translated forms were back-translated into English to verify the quality of translation, as well as consistency across the Gujarati and Hindi versions.

Statistical analyses

All statistical analyses were conducted using Stata 12.0 statistical software [19]. We conducted exploratory data analyses on household characteristics, caregiver diarrhea management knowledge, and diarrhea careseeking and treatment practices for both typical diarrheal episodes and episodes experienced in the two–weeks prior to the survey. For each state, we stratified responses by the experience of diarrhea in the preceding two–weeks and conducted t–tests and χ^2 tests to assess the equivalence of survey responses between the baseline and endline populations.

To address the main evaluation question of whether ORS and zinc treatment of children with diarrhea in the two– weeks preceding the survey increased from baseline to endline, we constructed state–specific logistic regression models to compute crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for the receipt of ORS/zinc by study phase (ie, endline vs baseline). We employed generalized estimating equations (GEE) with the logit link function and an independent correlation structure to adjust for village–level clustering [20]. We identified potential confounders for inclusion in multivariable models on the basis of *a priori* knowledge and bivariate analyses showing an association with both study phase and the receipt of ORS/zinc. The final multivariable models included indicators of child's sex, child's age >1 year and caregiver's education ≥1 year of schooling. Additionally, the ORS models included indicators of receipt of zinc and report of *pani ki kami*, a local term for dehydration; and the zinc models included an indicator of receipt of ORS and a continuous variable for maximum stool frequency in stools per day.

All models also included a categorical variable for careseeking, which was defined as no careseeking, private sector careseeking or public sector careseeking. We conducted a sensitivity analysis to assess how to best categorize the careseeking variable for the small proportion of caregivers who utilized both private and public sector sources. The results showed no statistically significant difference in the adjusted odds ratios between models allocating this small population into its own public/private sector careseeking category as compared to the private sector or the public sector categories. Given the comparable results, we opted to simplify the model by not adding an additional public/ private sector category. To help stabilize relatively small frequencies of public sector careseekers, we opted to include caregivers who sought care through both sectors in the public sector careseeking category.

There were no missing values for key dependent and explanatory variables. We tested all models for interaction between the study phase and careseeking variables. For final models, we confirmed the adequacy of fit using the Hosmer–Lemeshow test of goodness–of–fit [21].

RESULTS

Characteristics of caregivers, children and households

We collected baseline and endline data from 4200 and 5080 caregivers in Gujarat and from 3889 and 7853 caregivers in UP, respectively (**Figure 2** and **Figure 3**). In both states, the two–week diarrhea prevalence was higher at baseline than endline (Gujarat: 14.1% vs 10.9%, P<0.001; UP: 16.8% vs 12.7%, P<0.001). Characteristics of the caregiver, child and household were generally similar between baseline and endline in both states (**Table 1**). On average, caregivers at endline reported approximately one additional year of schooling compared to those at baseline in both states (P<0.001). In both states, the mean age and the ratio of male–to–female children were statistically significant-

Table 1. Characteristics of the primary caregiver, index child and household at baseline and endline, stratified by whether diarrhea was experienced by the index child in the two-weeks nreceding the survey

	No diarrhea	No diarrhea in the last two-weeks	vo-weeks	Diarrhea i	Diarrhea in the last two-weeks	o-weeks	No diarrhe	No diarrhea in the last two-weeks	vo-weeks	Diarrhea	Diarrhea in the last two-weeks	'o-weeks
	0	(mumber, %)		0	(number, %)			(mumber, %)			(number, %)	
	Baseline	Endline	P -value*	Baseline	Endline	P -value*	Baseline	Endline	P -value*	Baseline	Endline	P -value*
	(N=3606)	(N = 4527)		(N = 594)	(N = 553)		(N = 3237)	(N = 6852)		(N = 652)	(N = 1001)	
Primary caregiver:†												
Education in years of schooling:												
–Mean (SD)	3.9 (4.4)	4.6 (4.5)	<0.001 #	3.5 (4.2)	4.3 (4.3)	0.001‡	3.0 (4.4)	4.4 (5.0)	<0.001 #	2.7 (4.1)	3.8 (4.6)	<0.001
–Median (range)	2 (0, 22)	5 (0, 18)		0 (0, 17)	4 (0, 15)		0 (0, 19)	2 (0,19)		0 (0, 18)	0 (0, 17)	
Never attended school	1726 (47.9)	1848 (40.8)	<0.001	314 (52.9)	228 (41.2)	<0.001	2000 (61.8)	3365 (49.1)	<0.001‡	416 (63.8)	520 (52.0)	<0.001‡
Mean age in years (SD)	27.1 (5.4)	26.9 (4.7)	0.075	26.4 (4.9)	26.6 (4.4)	0.471	28.6 (6.0)	28.2 (5.4)	<0.001 #	28.0 (5.5)	27.5 (4.9)	0.052
Index child:†												
Male	1982 (55.0)	2562 (56.6)	0.141	304 (51.2)	297 (53.7)	0.392	1723 (53.2)	3710 (54.1)	0.389	336 (51.5)	536 (53.6)	0.423
Mean age of child in months (SD)	25.5 (16.0)	24.4 (15.0)	0.001‡	16.7 (12.6)	20.3 (14.1)	<0.001	26.0 (16.0)	26.2 (15.7)	0.445	18.6(13.6)	18.8 (13.5)	0.763
Household:												
Father's years of schooling: Mean (SD)	7.1 (5.6)	7.7 (4.4)	<0.001 #	6.8 (4.4)	7.5 (4.0)	0.005‡	6.1 (4.9)	6.9 (5.0)	<0.001 #	5.9 (4.7)	6.3 (4.8)	0.118
Father's years of schooling: Median (Range)	8 (0, 20)	9 (0, 20)		7 (0, 19)	8 (0, 21)		7 (0, 20)	8 (0, 22)		7 (0, 18)	8 (0, 19)	
Purified drinking water	2954 (81.9)	3475 (76.8)	<0.001‡	467 (78.6)	403 (72.9)	0.023‡	77 (2.4)	54 (0.8)	<0.001‡	11 (1.7)	6 (0.6)	0.032‡
Water on premises or <30 min to source	3119 (86.5)	3966 (87.6)	0.137	522 (87.9)	487 (88.1)	0.929	3209 (99.1)	6800 (99.2)	0.575	648 (99.4)	994 (99.3)	0.834
Household access to toilet facility§	809 (22.4)	1224 (27.0)	<0.001 #	97 (16.3)	114 (20.6)	0.061	599 (18.5)	1865 (27.2)	<0.001 #	107 (16.4)	222 (22.2)	0.004‡
BPL (below poverty line) card	1431 (39.7)	2164 (47.8)	<0.001‡	254 (42.8)	277 (50.1)	0.013	891 (27.5)	1547 (22.6)	<0.001 #	198 (30.4)	215 (21.5)	<0.001
Religion of father/ head of the household:			0.205			0.546			0.001‡			0.494
-Hindu	3443 (95.2)	4331 (95.7)		569 (95.8)	537 (97.1)		2865 (88.5)	5908 (86.2)		555 (85.1)	862 (86.1)	
Muslim	164 (4.6)	178 (3.9)		22 (3.7)	14 (2.5)		369 (11.4)	942 (13.8)		97 (14.9)	137 (13.7)	
-Other	9 (0.3)	18 (0.4)		3 (0.5)	2 (0.4)		3 (0.1)	2 (0.03)		0	2 (0.2)	
Ethnic group:			<0.001†			0.006			0.273			0.803
-Scheduled caste	434 (12.0)	754 (16.7)		79 (13.3)	110 (19.9)		1140 (35.2)	2510 (36.6)		235 (36.0)	377 (37.7)	
-Scheduled tribe	1088 (30.2) 1125 (24.9)	1125 (24.9)		200 (33.7)	165 (29.8)		7 (0.2)	7 (0.1)		0	0	
-Other backward caste	1495 (41.5)	2030 (44.8)		238 (40.1)	227 (41.1)		1546 (47.8)	3211 (46.9)		317 (48.6)	475 (47.5)	
-Other	589 (16.3)	618 (13.7)		77 (13.0)	51 (9.2)		544 (16.8)	1124 (16.4)		100 (15.3)	149 (14.9)	

group age Primary caregiver was the survey respondent. *Statistically significant at the P=0.05 level.

SIncludes households with own or shared access to one of the following facilities: flush; flush-to-piped-sewer; septic tank; pit latrine with or without slab/open pit. Households without toilet facilities reported open defecation.

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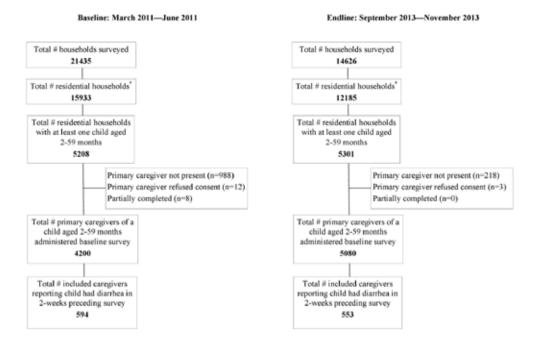


Figure 2. Survey profiles of the baseline and endline household surveys in Gujarat.

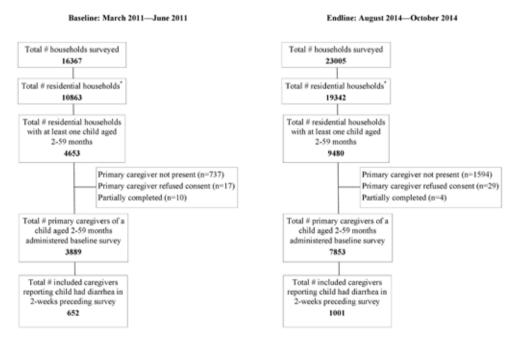


Figure 3. Survey profiles of the baseline and endline household surveys in Uttar Pradesh.

ly equivalent comparing baseline to endline. In Gujarat, the proportion of households with purified drinking water was high for both surveys but slightly fewer households had access at endline (76.3%) than baseline (81.5%; P<0.001). We observed the same trend in UP; although, the proportion of households reporting purified drinking water was

substantially lower in the state (2.3% at baseline vs 0.8% at endline; P<0.001). A larger proportion of households had access to a toilet facility at endline compared to baseline in both Gujarat (26.3% vs 21.6%, P<0.001) and UP (26.6% vs 18.2%, P<0.001). Additional characteristics of the study population are presented in **Table 1**.

Caregiver knowledge of diarrhea careseeking and treatment

Caregiver knowledge of appropriate sources of care for a child with diarrhea improved from baseline to endline in both states (Table 2). Awareness of private sector sources was high at baseline and experienced a moderate increase at endline (Gujarat: 92.6% vs 94.6%, P<0.001; UP: 98.4% vs 99.7%, P<0.001). In comparison to baseline, there was a large statistically significant increase in the proportion of caregivers who reported public sector sources as appropriate channels for diarrhea careseeking at endline in both states (Gurajat: 59.2% vs 89.1%, P<0.001; UP: 25.8% vs 76.7%, P<0.001); although, the absolute increase was more pronounced in UP (50.9%) than Gujarat (29.9%). In Gujarat, improved public sector awareness was largely driven by increased recognition of ASHAs (4.2% vs 44.2%, P < 0.001) and AWWs as appropriate sources of diarrhea treatment (15.5% vs 46.3%, P<0.001); whereas in UP, the shift was primarily driven by increased recognition of primary health centers (PHCs) (25.5% vs 71.9%, P<0.001) and, to a lesser degree, ASHAs (0.03% vs 17.9%, P<0.001).

We observed a statistically significant increase in ORS awareness from 53.7% at baseline to 76.0% at endline in Gujarat (P<0.001) (**Table 2**). In UP, ORS awareness decreased by an absolute difference of 4.7% (P<0.001) comparing baseline to endline. There was a statistically significant increase in the proportion of caregivers who had seen or heard of zinc and, without prompting, recognized it as a treatment for diarrhea in both Gujarat (4.5% vs 23.2%; P<0.001) and UP (5.6% vs 30.7%; P<0.001). In both states, higher zinc awareness at endline was attributed to increased report of public sector sources of information on zinc as a treatment for diarrhea. In **Table 2**, we report additional data on caregiver knowledge of diarrhea careseek-

ing and treatment stratified by report of diarrhea in the two–weeks prior to the survey; the trends were similar comparing caregivers with and without a recent diarrheal episode.

Careseeking and treatment of recent diarrheal episodes

The reported characteristics of diarrheal episodes occurring in the two–weeks preceding the survey were generally similar at baseline and endline in both states (**Table 3**). In Gujarat, *pani ki kami* (a local term for dehydration), lethargy/ irritability and sunken eyes were less frequently reported at endline (P<0.001). In UP, vomiting and sunken eyes were less common episode characteristics at endline (P<0.001), and mean maximum stool frequency decreased by 1.3 stools/d (P<0.001).

The proportion of caregivers who sought care outside the home for their child's diarrhea increased slightly from baseline to endline in Gujarat (67.0% vs 74.5%, *P*=0.005) but did not change in UP (87.7% vs 85.4%, P=0.178) (Table 3). There was a statistically significant increase in public sector careseeking in both states, although the trend was more pronounced in Gujarat (19.6% vs 37.6%, P<0.001; Figure 4) compared to UP (4.4% vs 9.1%, P<0.001; Figure 5). There was a borderline statistically significant decrease in private sector careseeking in Gujarat (80.2% vs 74.3%, *P*=0.046) but no change in UP (93.0% vs 90.4%, P = 0.086). The shift in careseeking was characterized by increased attendance at ASHAs and AWWs in Gujarat and ASHAs and PHCs in UP. In Gujarat, the overall decrease in private sector utilization was driven by reduced use of private hospitals/nursing homes, chemists and general stores, despite a slight increase in use of private providers.

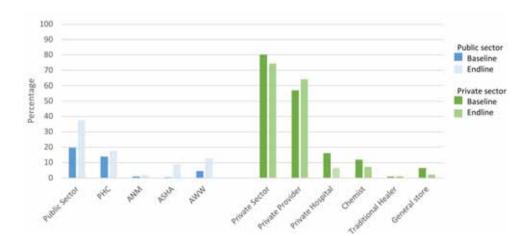


Figure 4. Sources of diarrhea careseeking at baseline and endline in Gujarat. Public sector includes: primary health centers, auxiliary nurse midwives, Accredited Social Health Activities and Anganwadi workers; private sector includes: private providers, private hospitals, chemists, traditional healers and general stores.

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Table 2. Caregiver knowledge of diarrhea careseeking and treatment, stratified by whether diarrhea was experienced by the index child in the two-weeks preceding the survey

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		No diarrhe	a in the last tv	vo weeks	Diarrhea	in the last tw	o weeks	No diarrhe	a in the last t	wo weeks	Diarrhea	Diarrhea in the last two weeks	o weeks
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(N=350) (N=350) (N=531) (N=531) (N=331) (N=31) (N=31) (N=31) (N=31) (N=31) (N=331) (N=31) (N=331) (N=331) (N=331) (N=331) (N=331) (N=331) (N=331) (N=331) (N=331) (N=321) (N=31) (N=321) (N=31) (N=321) (N=31) (N=31) (N=31) (N=31) (N=31) <th></th> <th>Baseline</th> <th>Endline</th> <th>P-value*</th> <th>Baseline</th> <th>Endline</th> <th>P-value*</th> <th>Baseline</th> <th>Endline</th> <th>P-value*</th> <th>Baseline</th> <th>Endline</th> <th><i>P</i>-value*</th>		Baseline	Endline	P-value*	Baseline	Endline	P -value*	Baseline	Endline	P-value*	Baseline	Endline	<i>P</i> -value*
Appropriate sources of care for a child with diarrher: Appropriate sources of care for a child with diarrher: Public scene source: 2123 (53.0) 418 (75.6) 400.011 833 (50.1) 515 (53.1) 80011 833 (55.5) 8983 (71.5) Public scene source: 237 (71.0) 3312 (32.0) 313 (53.0) 418 (75.6) 400.011 815 (75.6) 50011 816 (75.6) 823 (95.7) -Mustlingy tunes midwide: 237 (71.0) 553 (54.4) 2010 (44.4) <00011 517 (51.9) 00011 216 (75.6) 420.0011 216 (77.6) 52014.7 1268 (82.9) 67001 110.3 1268 (95.7) 67006 1263 (95.9) 67001 110.3 2164.7 -Mustlingy tunes midwide 2349 (92.9) 4283 (94.1) 00011 215 (95.9) 6900 (10.0) 1878 (27.4) -Mustling transmatic weater 1330 (92.9) 430011 100.32 200011 216.7 216.7 216.7 216.7 216.7 216.7 216.7 216.7 216.7		(N = 3606)	(N = 4527)		(N = 594)	(N = 553)		(N=3237)	(N = 6852)		(N = 652)	(N = 1001)	
Public sector source 2123 (58.9) 4010 (88.6) < 00011 315 (93.1) < 00011 834 (25.8) $< 2297 (76.3)$ $< 2297 (76.3)$ $< 2297 (71.3)$ < 20011 $< 125 (33.0)$ $< 181 (75.6)$ < 20011 $< 237 (71.3)$ < 20011 $< 237 (71.3)$ < 20011 $< 214 (75.3)$ < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 20011 < 200011 $< 210 (70.1)$ < 200011 $< 210 (70.1)$ < 200011 $< 210 (70.1)$ < 200011 $< 210 (70.1)$ < 200011 $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$ $< 210 (70.1)$	Appropriate sources of care for a child with dia	arrhea:†											
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		2123 (58.9)	4010 (88.6)	<0.001‡	363 (61.1)	515 (93.1)	<0.001 #	834 (25.8)	5229 (76.3)	<0.001‡	168 (25.8)	791 (79.0)	<0.001 #
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	–PHC/Government hospital	1837 (50.9)	3312 (73.2)	<0.001‡	315 (53.0)	418 (75.6)	<0.001 #	825 (25.5)	4898 (71.5)	<0.001‡	167 (25.6)	748 (74.7)	<0.001‡
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		257 (7.1)	508 (11.2)	<0.001‡	45 (7.6)	62 (11.2)	0.034‡	11 (0.3)	109 (1.6)	<0.001‡	1 (0.2)	18 (1.8)	0.002#
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		159 (4.4)	2010 (44.4)	<0.001‡	19 (3.2)	234 (42.3)	<0.001 #	1 (0.03)	1248 (18.2)	<0.001	0	157 (15.7)	<0.001‡
Private sector source $3340(92.9)$ $4287(94.7)$ $60.01\ddagger$ $551(92.8)$ $519(93.9)$ 6461 $318(198.3)$ $6828(99.7)$ -Private bospital/nursing home $1539(47.2)$ $3735(33.6)$ $60.001\ddagger$ $461(77.6)$ $471(85.2)$ $0.011\ddagger$ $313(96.9)$ $673(95.9)$ -Private loopital/nursing home $138(35.1)$ $10961(35.2)$ $60.01\ddagger$ $413(15)$ $0001\ddagger$ $223(40)$ 0001 -Traditional heler $18(0.5)$ $313(3.5)$ $494(3.3)$ $60.001\ddagger$ $147(3.15)$ $0001\ddagger$ $223(40)$ $20(7)$ -Traditional heler $18(0.5)$ $32(0.7)$ 0.716 $13(2.2)$ $6(1.1)$ 0.143 $22(0.0)$ $3(0.0)$ -Gharitable hospital/NGO/Tinst $28(8)$ $32(0.7)$ 0.716 $3(2.2)$ $6(1.1)$ 0.143 $22(0.0)$ $3(0.0)$ -Mobile clinic $44(1.2)$ $64(1.4)$ 0.716 $312(53.0)$ $46(84.3)$ $6(001)$ $197(61)$ -Mobile clinic $144(1.2)$ $64(1.4)$ $0.701\ddagger$ $315(53.0)$ $46(84.3)$ $6(001)$ $197(62)$ $22(23)$ Avare of Stor duarthea treatments $103(4.5)$ $976(21.6)$ $0.001\ddagger$ $315(53.0)$ $466(84.3)$ $6(001)$ $197(61.5)$ $22(23)$ Avare of Stor duarthea treatments $103(4.5)$ $976(21.6)$ $0.001\ddagger$ $315(53.0)$ $466(84.3)$ $6(001)$ $197(61.5)$ $22(29)$ Avare of Stor duarthea treatments $103(4.5)$ $976(21.6)$ $976(21.6)$ $200(35.2)$ $200(35.2)$ $200(35.2)$ Avare of St		555 (15.4)	2063 (45.6)	<0.001‡	94 (15.8)	287 (51.9)	<0.001‡	2 (0.06)	322 (4.7)	<0.001‡	0	42 (4.2)	<0.001‡
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Private sector source	3340 (92.9)		<0.001‡	551 (92.8)	519 (93.9)	0.461	3181 (98.3)	6828 (99.7)	<0.001‡	644 (98.8)	(8.66) 666	<0.001‡
Private hospital/nursing home 1539 (42.7) 1059 (23.4) 0.001 224 (37.7) 129 (23.3) 0.001 232 (10.0) 1878 (27.4) Chemist 138 (0.5) 147 (3.3) 0.001 5 (0.0) 22 (4.0) 0.01 21 (0.0) 1878 (27.4) Traditional healer 138 (0.5) 147 (3.3) 0.001 5 (0.8) 22 (4.0) 0.01 21 (0.0) 81 (1.2) Charitable hospital/NGO/Tust 28 (0.8) 32 (0.7) 0.716 13 (2.2) 6 (1.1) 0.143 2 (0.0) 3 (0.4) Mobile clinic 44 (1.2) 64 (1.4) 0.449 4 (0.7) 8 (1.5) 0.001 19 (0.6) 19 (0.6)	-Private provider	2784 (77.2)	3785 (83.6)	<0.001#	461 (77.6)	471 (85.2)	0.001 #	3136 (96.9)	6730 (98.2)	<0.001	631 (96.8)	983 (98.2)	0.063
-Chemist 138 (3.8) 1494 (3.3.0) 6.001 ; $14.2.4$) $174 (31.5)$ 0.001 ; $22 (0.7)$ $2515 (36.7)$ -Traditional healer 18 (0.5) $147 (3.3)$ 6.001 ; $5 (0.8)$ $22 (4.0)$ 0.001 ; 0.0001 ; 0.001 ; 0.0001 ;	-Private hospital/nursing home	1539 (42.7)	1059 (23.4)	<0.001#	224 (37.7)	129 (23.3)	0.001 #	323 (10.0)	1878 (27.4)	<0.001	76 (11.7)	283 (28.3)	<0.001‡
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		138 (3.8)		<0.001‡	14 (2.4)	174 (31.5)	0.001 #	22 (0.7)	2515 (36.7)	<0.001‡	3 (0.5)	437 (43.7)	<0.001‡
	-Traditional healer	18 (0.5)	147 (3.3)	<0.001\$	5 (0.8)	22 (4.0)	0.001 #	0	81 (1.2)	<0.001\$	0	21 (2.1)	<0.001
		28 (0.8)	32 (0.7)	0.716	13 (2.2)	6 (1.1)	0.143	2 (0.06)	3 (0.04)	0.705	0	0	1
Aware of ORS for diarrhea treatment\$ 1942 (53.9) 337 (75.0) 60.01 # $15 (53.0)$ $466 (84.3)$ $c0.01$ # $265 (82.9)$ $5399 (78.8)$ Aware of zinc for diarrhea treatment\$ $163 (4.5)$ $976 (21.6)$ $c0.001$ # $26 (4.4)$ $200 (36.2)$ $c0.001$ # $168 (5.2)$ $2022 (29.5)$ -If yes, source of zinc awareness:†# $=$ $39 (23.9)$ $769 (78.8)$ $c0.001$ # $4(15.4)$ $155 (77.5)$ $c0.001$ # $194 (71.7)$ -Public sector source $136 (83.4)$ $540 (55.3)$ $c0.001$ # $4(15.4)$ $155 (77.5)$ $c0.01$ # $194 (71.7)$ -Media (amouncement, radio, poster/wall paint- $1(0.6)$ $84 (8.6)$ $c0.001$ # $24 (92.3)$ $111 (5.5)$ 0.200 $5 (3.0)$ $92 (4.6)$ -Media (amouncement, radio, poster/wall paint- $1(0.6)$ $84 (8.6)$ $c0.001$ # $24 (92.3)$ $111 (5.5)$ 0.200 $92 (4.6)$ -Media (amouncement, radio, poster/wall paint- $1(0.6)$ $84 (8.6)$ $c0.001$ # $12 (10.2)$ $87 (10.1)$ -Media (amouncement, radio, poster/wall paint- $1(0.6)$ $84 (8.6)$ $c0.001$ # $11 (5.5)$ 0.200 </td <td>-Mobile clinic</td> <td>44 (1.2)</td> <td>64 (1.4)</td> <td>0.449</td> <td>4 (0.7)</td> <td>8 (1.5)</td> <td>0.198</td> <td>19 (0.6)</td> <td>195 (2.9)</td> <td><0.001</td> <td>2 (0.3)</td> <td>12 (1.2)</td> <td>0.053</td>	-Mobile clinic	44 (1.2)	64 (1.4)	0.449	4 (0.7)	8 (1.5)	0.198	19 (0.6)	195 (2.9)	<0.001	2 (0.3)	12 (1.2)	0.053
Aware of zinc for diarrhea treatment§ 163 (4.5) 976 (21.6) <0.001‡ 26 (4.4) 200 (36.2) <0.001‡ 168 (5.2) 2022 (29.5) -If yes, source of zinc awareness:†,#	Aware of ORS for diarrhea treatment§	1942 (53.9)		<0.001‡	315 (53.0)	466 (84.3)	<0.001‡	2685 (82.9)	5399 (78.8)	<0.001	561 (86.0)	787 (78.6)	<0.001‡
If yes, source of zinc awareness; # -Public sector source $39(23.9)$ $769(78.8)$ <0.001 # $19(11.3)$ $739(36.6)$ -Private sector source $136(83.4)$ $540(55.3)$ <0.001 # $12(56.0)$ <0.001 # $19(11.3)$ $739(36.6)$ -Media (amouncement, radio, poster/wall paint- $1(0.6)$ $84(8.6)$ <0.001 # 0 $11(5.5)$ 0.220 $5(3.0)$ $92(4.6)$ -Media (amouncement, radio, poster/wall paint- $1(0.6)$ $84(8.6)$ <0.001 # 0 $11(5.5)$ 0.220 $5(3.0)$ $92(4.6)$ -Meighbor/relative $1(0.6)$ $47(4.8)$ <0.001 # 0 $11(5.5)$ 0.220 $2(14.9)$ $187(19.1)$ NGO - non-governmental organizations $1(0.6)$ $47(4.8)$ <0.001 # 0 $11(5.5)$ 0.220 $25(14.9)$ $187(19.1)$ NGO - non-governmental organizations *P-values were generated comparing baseline and endline values in Stata 12.0 using t-tests of equivalence for continuous variables and χ^2 tests (or Fischer's nary and categorical variables [19]. *P-values were generated comparing baseline and endline values in Stata 12.0 using t-tests of equivalence for continuous variables and χ^2 tests (or Fischer's nary and categorical varia	Aware of zinc for diarrhea treatment§	163 (4.5)	976 (21.6)	<0.001‡	26 (4.4)	200 (36.2)	<0.001‡	168 (5.2)	2022 (29.5)	<0.001	51 (7.8)	389 (38.9)	<0.001‡
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	-If yes, source of zinc awareness:†,#												
-Private sector source 136 (83.4) 540 (55.3) <0.001 137 (81.6) 1449 (71.7) -Media (amnouncement, radio, poster/wall paint- 1 (0.6) 84 (8.6) <0.001 11 (5.5) 0.220 $5 (3.0)$ $92 (4.6)$ ing, pamphlet, television) $-Neighbor/relative$ $1 (0.6)$ $47 (4.8)$ <0.001 0 $11 (5.5)$ 0.220 $5 (3.0)$ $92 (4.6)$ NGO - non-governmental organizations $1 (0.6)$ $47 (4.8)$ <0.001 0 $11 (5.5)$ 0.220 $5 (14.9)$ $187 (19.1)$ NGO - non-governmental organizations $*$ $*$ -values were generated comparing baseline and endline values in Stata 12.0 using t-tests of equivalence for continuous variables and χ^2 tests (or Fischer's nary and categorical variables [19]. $*$ <	Public sector source	39 (23.9)	769 (78.8)	<0.001‡	4 (15.4)	155 (77.5)	<0.001‡	19 (11.3)	739 (36.6)	<0.001‡	7 (13.7)	107 (27.5)	0.035‡
$\begin{array}{l lllllllllllllllllllllllllllllllllll$	-Private sector source	136 (83.4)	540 (55.3)	<0.001‡	24 (92.3)	112 (56.0)	<0.001	137 (81.6)	1449 (71.7)	0.006‡	40 (78.4)	303 (77.9)	0.930
mg, paraptict, tarevisiony 1 (0.6) 47 (4.8) <0.001 \ddagger 0 11 (5.5) 0.220 25 (14.9) 187 (19.1) NGO - non-governmental organizations NGO - non-governmental organizations $*$ P-values were generated comparing baseline and endline values in Stata 12.0 using t-tests of equivalence for continuous variables and χ^2 tests (or Fischer ^t nary and categorical variables [19]. *Respondents could supply more than one answer; column percentage totals may exceed 100%. $\$$ Statistically significant at the $P=0.05$ level.	-Media (announcement, radio, poster/wall paint-	1 (0.6)	84 (8.6)	<0.001 #	0	11 (5.5)	0.220	5 (3.0)	92 (4.6)	0.341	5 (9.8)	13 (3.3)	0.029‡
NGO – non-governmental organizations NGO – non-governmental organizations *P-values were generated comparing baseline and endline values in Stata 12.0 using t-tests of equivalence for continuous variables and χ^2 tests (or Fischer's nary and categorical variables [19]. †Respondents could supply more than one answer; column percentage totals may exceed 100%. ‡Statistically significant at the $P=0.05$ level.	(1101614	1 (0.6)	47 (4.8)	<0.001 #	0	11 (5.5)	0.220	25 (14.9)	(161) 187	0.175	3 (5 9)	83 (21.3)	<0.009
nary anu categoricat variances (19). †Respondents could supply more than one answer; column percentage totals may exceed 100%. ‡Statistically significant at the P=0.05 level.	NGO – non–governmental organizations *P–values were generated comparing baseline and	l endline value	s in Stata 12.0	using t-test	s of equivaler	ice for continu	uous variabl	es and χ^2 tests	or Fischer's (exact tests in	the case of lo	w cell frequer	icies) for bi-
\pm Statistically significant at the <i>P</i> =0.05 level.	Trany and categorized variables [17].	r; column perc	entage totals n	1 iay exceed	.%00								
SRespondents were considered aware of ORS/zinc for diarrhea treatment if they reported having seen or heard the products prior to the survey and responded (unprompted) that ORS/zinc were used for diarrhea	*Statistically significant at the P=0.05 level. §Respondents were considered aware of ORS/zinc i	for diarrhea ti	eatment if they	reported h	tving seen or]	neard the pro	ducts prior 1	o the survey a	nd responded	(unprompte	d) that ORS/z	inc were used	for diarrhea

treatment.

#Percentages based on denominator of total aware of zinc for diarrhea treatment.

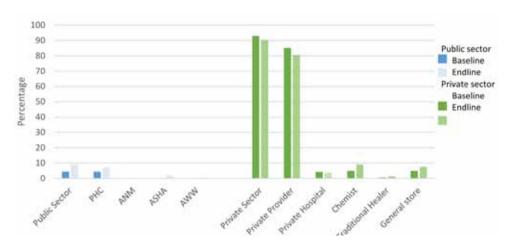


Figure 5. Sources of diarrhea careseeking at baseline and endline in Uttar Pradesh. Public sector includes: primary health centers, auxiliary nurse midwives, Accredited Social Health Activities and Anganwadi workers; private sector includes: private providers, private hospitals, chemists, traditional healers and general stores.

In Gujarat, the proportion of diarrheal episodes treated with ORS increased from 15.3% at baseline to 39.6% at endline (P<0.001) (**Table 3**). In UP, there was no difference in ORS coverage at endline (20.2%) compared to baseline (21.6%, P=0.485). Zinc treatment was statistically significantly higher at endline than baseline in both Gujarat (2.5% vs 22.4%, P<0.001) and UP (3.1% vs 7.0%, P<0.001). The same trend was observed in the number of episodes treated with both ORS and zinc (0.5% vs 18.4%, P<0.001 in Gujarat and 1.2% vs 3.3%, P<0.001 in UP).

There was a statistically significant increase in the proportion of children treated with antidiarrheals from baseline to endline in UP (5.2% vs 21.9%, P<0.001) and Gujarat (2.6% vs 42.6%, P<0.001; **Table 3**). This shift was driven by comparable increases in treatment with antidiarrheals through both the public and private sectors (data not shown). Among children who sought care in Gujarat, the proportion treated with antidiarrheals increased from 7.7% to 21.3% in the public sector (P<0.001); in UP, this figure increased from 4.0% to 48.7% in the public sector (P<0.001) and from 2.4% to 43.7% in the private sector (P<0.001).

Compared to baseline, the proportion of children administered antibiotics was higher at endline in Gujarat (16% vs 32%, P<0.001) but not in UP (28.2% vs 30.8%, P=0.259; **Table 3**). Unlike the trend in antidiarrheals, the increase in antibiotics observed in Gujarat was solely driven by a rise in the proportion of children receiving antibiotics through the private sector (ie, 25.1% at baseline vs 50.3% at endline), as receipt of antibiotics through the public sector did not change between baseline and endline (ie, 23.1% vs 27.1%) (data not shown). Additional data on careseeking and treatment are provided in **Table 3**.

Factors associated with ORS treatment

In bivariate analysis of the odds of ORS treatment at endline compared to baseline, there was a statistically significant increase in Gujarat (OR=3.6, 95% CI 2.7–4.8) and a non–statistically significant decrease in UP (OR=0.90, 95% CI 0.7–1.2) (**Table 4**).

In multivariable analysis, there was a statistically significant interaction between the study phase and careseeking variables in Gujarat (P=0.009). The adjusted odds (aOR) of ORS treatment at endline compared to baseline were elevated by a factor of 4.7 (95% CI 1.3–17.5) among children with no careseeking, by 1.6 (95% CI 1.1–2.4) among those with private sector careseeking and by 4.7 (95% CI 2.5–9.0) among those with public sector careseeking (**Table 4**). Among children for whom no care was sought, the higher odds of ORS treatment at endline compared to baseline were attributable to an increase in the proportion of caregivers who reported having ORS product at home. The adjusted odds of ORS treatment were higher among children who also received zinc (aOR=4.3, 95% CI 2.6–7.0).

In UP, there was no interaction between the study phase and careseeking variables in multivariable analysis. The adjusted OR of ORS treatment comparing endline to baseline was 0.8 (95% CI 0.6–1.0) (**Table 4**). Compared to no careseeking, the adjusted odds of ORS treatment were 3.9 (95% CI 2.2–6.9) times higher among those who sought care from a private sector source and 7.8 (95% CI 3.9–15.7) times higher among those who sought public sector care. The adjusted odds of ORS treatment were elevated by a factor of 2.7 (95% CI 1.7–4.2) among zinc–treated children.

Factors associated with zinc treatment

The unadjusted odds of zinc treatment were statistically significantly higher at endline compared to baseline in both

Table 3. Careseeking and treatment of diarrheal episodes occurring in the two-weeks preceding the survey

	(Gujarat (No., %)		UTT	ar P radesh (No., ^c	%)
	Baseline	Endline	P -value*	Baseline	Endline	P -value*
	(N=594)	(N=553)		(N = 652)	(N = 1001)	
Episode characteristics:						
Blood in stools	44 (7.4)	34 (6.2)	0.397	108 (16.6)	166 (16.6)	0.985
Fever	370 (62.3)	318 (57.5)	0.098	543 (83.3)	859 (85.9)	0.147
Vomiting	218 (36.7)	199 (36.0)	0.801	377 (57.8)	377 (37.7)	< 0.001**
Pani ki kami (local term for dehydration)	268 (45.1)	167 (30.2)	<0.001†	344 (52.8)	573 (57.3)	0.070
Lethargy/irritability	382 (64.3)	245 (44.3)	<0.001†	487 (74.7)	780 (78.0)	0.120
Sunken eyes	156 (26.3)	48 (8.7)	<0.001†	271 (41.6)	300 (30.0)	< 0.001**
Maximum stool frequency (stools/d)						
Mean (SD)	4.8 (1.5)	4.8 (1.4)	0.835	6.6 (3.1)	5.3 (2.1)	< 0.001**
Median (range)	4 (3, 13)	4 (3, 10)		6 (3, 30)	5 (3, 25)	
Sought care outside the home	398 (67.0)	412 (74.5)	0.005†	572 (87.7)	855 (85.4)	0.178
If yes, source of careseeking: [‡] , [§]						
Public sector source	79 (19.6)	155 (37.6)	< 0.001†	25 (4.4)	78 (9.1)	< 0.001†
-Primary health center/Government hospital	55 (13.8)	72 (17.5)	0.153	25 (4.4)	59 (6.9)	0.047†
–Auxiliary nurse midwife	4 (1.0)	8 (1.9)	0.270	0	1 (0.1)	0.413
-Accredited social health activist (ASHA)	2 (0.5)	37 (9.0)	<0.001†	0	16 (1.9)	0.001†
–Anganwadi Worker (AWW)	18 (4.5)	53 (12.9)	<0.001†	1 (0.2)	3 (0.4)	0.538
Private sector source	319 (80.2)	306 (74.3)	0.046†	532 (93.0)	773 (90.4)	0.086
-Private provider	227 (57.0)	264 (64.1)	0.040†	487 (85.1)	689 (80.6)	0.027†
-Private hospital/Nursing home	64 (16.1)	27 (6.6)	< 0.001†	24 (4.2)	32 (3.7)	0.666
-Chemist	47 (11.8)	30 (7.3)	0.028†	28 (4.9)	77 (9.0)	0.004†
-Traditional healer#	4 (1.0)	5 (1.2)	0.777	3 (0.5)	11 (1.3)	0.152
-Charitable hospital/NGO/Trust	5 (1.3)	3 (0.7)	0.447	0	1 (0.1)	0.413
–Mobile clinic	1 (0.3)	1 (0.3)	0.981	1 (0.2)	4 (0.5)	0.359
–General store	26 (6.5)	9 (2.2)	0.003†	28 (4.9)	64 (7.5)	0.050
Administered treatment:						
Any treatment	418 (70.4)	429 (77.6)	0.006†	582 (89.3)	911 (91.0)	0.244
ORS¶	91 (15.3)	219 (39.6)	< 0.001†	141 (21.6)	202 (20.2)	0.485
Zinc¶	15 (2.5)	124 (22.4)	< 0.001†	20 (3.1)	70 (7.0)	< 0.001†
ORS and zinc¶	3 (0.5)	102 (18.4)	< 0.001 †	8 (1.2)	33 (3.3)	0.008†
Antibiotics	95 (16.0)	177 (32.0)	< 0.001 †	184 (28.2)	308 (30.8)	0.259
Antidiarrheal	31 (5.2)	121 (21.9)	<0.001†	17 (2.6)	426 (42.6)	< 0.001†
Syrup, unknown	132 (22.2)	51 (9.2)	<0.001†	127 (19.5)	113 (11.3)	< 0.001†
Tablet, unknown	213 (35.9)	57 (10.3)	< 0.001†	165 (25.3)	282 (28.2)	0.196
Powder, unknown	47 (7.9)	10 (1.8)	< 0.001†	213 (32.7)	4 (0.4)	< 0.001†
Injection	40 (6.7)	12 (2.2)	< 0.001†	165 (25.3)	125 (12.5)	< 0.001†
IV Fluids	5 (0.8)	8 (1.5)	0.334	13 (2.0)	2 (0.2)	< 0.001†

ORS - oral rehydration salts, NGO - non-governmental organization, IV - intravenous

**P*-values were generated comparing baseline and endline values in Stata 12.0 using t-tests of equivalence for continuous variables and χ^2 tests (or Fischer's exact tests in the case of low cell frequencies) for binary and categorical variables (16).

†Statistically significant at the P = 0.05 level.

‡Respondents could supply more than one answer; column percentage totals may exceed 100%.

*Percentages based on denominator of total who sought care outside the home.

#Includes Ayurvedic, Vaid, Homepathic, Hakim, Unani.

[ORS category includes children who received ORS with or without zinc and vice versa. ORS and zinc category includes children who received both products.

Gujarat (OR=11.2, 95% CI 6.4–19.3) and UP (OR=2.4, 95% CI 1.4–3.9) (**Table 4**). In multivariable analysis, the effect of study phase was not modified by careseeking in either state.

In Gujarat, the adjusted OR comparing zinc treatment at endline to baseline was 7.3 (95% CI 4.1–13.0) (**Table 4**). The adjusted ORs comparing zinc treatment among chil-

dren with private and public sector careseeking relative to no careseeking were 12.2 (95% CI 2.9–51.6) and 26.5 (95% CI 6.1–114.7), respectively. In UP, the adjusted odds of zinc treatment were 2.5 (95% CI 1.5–4.4) times higher at endline compared to baseline and were elevated among children with private sector (aOR=3.1, 95% CI 1.0–10.1) and public sector careseeking (aOR=9.5, 95% CI 2.7–

Table 4. Bivariate and multivariate Generalized Estimating Equations* analyses of the association between study phase and receipt of
ORS and zinc treatment among children with diarrhea in the two–weeks preceding the survey

GUJARAT				UTTAR PRADESH							
OUTCOME – RECEIPT OF ORS:											
	Unadjusted OR (95% CI)	P–value	Adjusted OR (95% CI)†	<i>P</i> –value	Unadjusted OR (95% CI)	P–value	Adjusted OR (95% CI)†	<i>P</i> –value			
Phase of study											
– Endline	3.6 (2.7–4.8)	<0.001‡			0.9 (0.7–1.2)	0.485	0.8 (0.6–1.0)	0.058			
– Baseline	1.0				1.0		1.0				
Careseeking:											
– Public Sector	53.6 (28.8–99.5)	<0.001‡			10.8 (5.5–21.5)	<0.001‡	7.8 (3.9–15.7)	<0.001‡			
– Private Sector	7.8 (4.4–14.1)	<0.001‡			4.6 (2.6–8.1)	<0.001‡	3.9 (2.2–6.9)	<0.001‡			
– No careseeking	1.0				1.0		1.0				
Endline vs Baseline:*											
– Public Sector	7.2 (3.9–13.3)	<0.001‡	4.7 (2.5–9.0)	<0.001‡							
– Private Sector	2.1 (1.4–3.1)	<0.001‡	1.6 (1.1–2.4)	0.036‡							
–No careseeking	4.9 (1.3–18.2)	0.017‡	4.7 (1.3–17.5)	0.021‡							
Receipt of zinc	12.1 (8.0–18.3)	<0.001‡	4.3 (2.6–7.0)	<0.001‡	3.5 (2.3–5.4)	<0.001‡	2.7 (1.7-4.2)	<0.001‡			
OUTCOME - RECEI	PT OF ZINC:										
	Unadjusted OR (95% CI)	P–value	Adjusted OR (95% CI)†	P–value	Unadjusted OR (95% CI)	P–value	Adjusted OR (95% CI)†	P–value			
Phase of study:											
– Endline	11.2 (6.4–19.3)	<0.001‡	7.3 (4.1–13.0)	<0.001‡	2.4 (1.4–3.9)	0.001‡	2.5 (1.5-4.4)	0.001‡			
– Baseline			1.0		1.0		1.0				
Careseeking:											
– Public Sector	87.6 (21.3–360.9)	<0.001‡	26.5 (6.1–114.7)	<0.001‡	16.8 (4.8–58.3)	<0.001‡	9.5 (2.7–33.6)	0.001‡			
– Private Sector	18.4 (4.5–75.7)	<0.001‡	12.2 (2.9–51.6)	0.001‡	4.0 (1.3–12.9)	0.019	3.1 (1.0–10.1)	0.059			
– No careseeking	1.0		1.0		1.0		1.0				
Receipt of ORS	12.1 (8.0–18.3)	<0.001‡	4.3 (2.6–7.0)	<0.001‡	3.5 (2.3–5.4)	<0.001‡	2.7 (1.7–4.3)	<0.001‡			

OR - odds ratio, CI - confidence interval, ORS - oral rehydration salts

*Generalized estimating equations (GEE) with the logit link function and an independent correlation structure used to generate semi-robust standard errors to adjust for multiple observations at the village-level in Stata 12.0 (16).

 \uparrow All multivariable analyses adjusted for the above–listed variables and: sex of child; age of child >1 y; and maternal education \ge 1 y of school. ORS model also adjusted for receipt of zinc and report of *pani ki kami* (local term for dehydration). Zinc model also adjusted for receipt of ORS and reported maximum stool frequency in stools/d.

*Statistically significant at the P = 0.05 level.

Statistically significant interaction between phase of the study and careseeking sector (P = 0.009).

33.6) relative to those who did not seek care. In both states, there was a statistically significant association between zinc treatment and receipt of ORS (P<0.001).

DISCUSSION

The external evaluation of the DAZT program showed that over the course of the program period, the odds of zinc treatment increased in both states, and the odds of ORS treatment increased in Gujarat but not UP. In both states, the odds of adequate treatment were higher among those who sought care outside the home, but the effect was greater in the public compared to the private sector. Between baseline and endline, zinc awareness and recognition of public sector providers as appropriate sources of diarrhea care increased in both Gujarat and UP, and ORS awareness increased in Gujarat. Among caregivers of children with diarrhea in the preceding two–weeks, public sector careseeking was higher at endline relative to baseline, but private sector careseeking remained high. There was a decrease in diarrhea prevalence from baseline to endline, but this shift was likely attributable to the timing of the surveys within different diarrhea seasons and not to the DAZT program.

The design of the prospective evaluation was quasi-experimental and thus our conclusions are based on pre-post comparisons between the DAZT districts at baseline and endline. The use of historical controls is not the gold standard in evaluation design, but state government plans to eventually scale-up ORS and zinc throughout all districts in Gujarat and UP during the project period precluded the use of non-DAZT districts as comparison areas. In order to reduce the bias introduced from a quasi-experimental design, we routinely monitored the DAZT districts and collected data on potential contextual factors. Through this documentation, we did not become aware of any overlap between the DAZT project and other diarrhea management or sanitation programs that may have influenced ORS and

Our findings show that over the course of the DAZT project, zinc coverage increased in both states and ORS coverage increased in Gujarat. However, the magnitude of the change was not as large as anticipated, with only 18.4% and 3.3% of diarrheal episodes treated with both ORS and zinc at endline in Gujarat and UP, respectively. The need for improved diarrhea treatment among children underfive in the project areas is therefore still evident. Nevertheless, increases in ORS and zinc awareness and shifts in the recognition and utilization of public sector channels for diarrhea careseeking are promising first steps in generating program impact. It should be noted that these changes occurred in the absence of caregiver demand generation activities. Given the DAZT program's sole focus on providerlevel activities, changes in caregiver knowledge and practices could only have resulted through word-ofmouth. In particular, the public sector approach, which operated on the theory that improving the quality of diarrhea treatment among public providers would lead to increases in diarrhea careseeking through public sector channels, depended on the message of improved care to naturally trickle into the community. Our results indicate that perceptions regarding the role of public sector providers in diarrhea treatment were beginning to evolve among caregivers of young children; however, we observed gaps between the awareness of the public sector as an appropriate source of treatment and the practice of public sector careseeking. Future programs should incorporate community-level behavior change communication to quickly disseminate messages regarding appropriate sources of diarrhea treatment and to maximize the impact of those messages on careseeking practices. Moreover, activities targeting caregivers should also focus on generating demand for ORS and zinc, in addition to increasing awareness.

The evaluation results highlight differences in diarrhea treatment by the sector through which care was sought. The odds of receiving ORS and zinc were higher among those who sought care through either sector compared to those who did not seek care outside the home, but the effect was greater in the public sector. There are vast differences between the public and private sector health systems that could have contributed to variations in program impact. The public sector program may have been better positioned to modify providers' diarrhea treatment practices because government employees are easily identifiable and can be required to attend trainings. In comparison, the private sector program had to contend with a large population of informal providers who were difficult to locate and at liberty to reject visits from program representatives. Despite the challenges associated with altering the diarrhea treatment practices of private providers, we observed only a gradual shift towards public sector careseeking with the overwhelming majority of caregivers continuing to seek care through private sources at endline, and thus future programmatic investment in the private sector is necessary and worthwhile.

The results of the evaluation underscored differences in the magnitude of change between states. In Gujarat, we observed absolute increases of 24.3% in ORS coverage and 19.9% in zinc coverage. In comparison, ORS coverage did not change and the absolute increase in zinc coverage was only 3.9% in UP. Since the odds of receiving ORS and zinc were higher in the public sector, it is possible that poorer coverage in UP compared to Gujarat was at least in part attributable to the relatively smaller increase in public sector careseeking (ie, 4.7% in UP vs 18.0% in Gujarat). There were also differences in the breakdown of public sector careseeking across specific provider cadres; careseeking to ASHAs and AWWs experienced absolute increases of more than 8% in Gujarat compared to 1.9% and 0.2% in UP. Future public sector programs in UP should focus on increasing the uptake of diarrhea careseeking through community-level ASHAs and AWWs.

The findings of this evaluation are potentially limited by the biases associated with caregiver report and recall. To reduce the threat of recall bias, we limited the assessment of diarrhea careseeking and treatment to episodes occurring within two-weeks preceding the survey, which is the widely accepted standard for large surveys [22]. In addition, we employed several methodological techniques to improve and confirm caregiver recall of diarrheal treatments given to children during the two-week period. During the interview, caregivers were shown laminated photos of commonly available diarrhea treatment products in an attempt to prompt recall of what had been administered to the child. Interviewers also checked all available packaging and recorded the product details. We increased our efforts to identify packaging at endline as an added precaution against misidentification of ORS and zinc; if packaging was torn and the brand name illegible, the interviewers brought the remnants to local chemists for assistance determining the identity of the product. As a result of the enhanced methods at endline, unknown treatments largely decreased in both states. Though a fraction of products could not be identified despite the added measures taken at endline, these were unlikely to have been zinc since the zinc product or packaging for a 10 to 14-day regimen would have been available in the household for episodes occurring within two weeks of the survey.

We observed an increasing trend in antidiarrheals and antibiotics from baseline to endline that is likely an artefact of the additional treatment identification methods employed at endline. It is possible that the revised methods, which resulted in an overall lower percentage of unknown products, produced an apparent increase in products identified as antidiarrheals and antibiotics. However, it is also possible that through heightened attention to diarrhea management, providers were not only more likely to advise ORS and zinc but also other misguided treatments. Future programs should be aware of this risk and focus efforts on warning providers of the dangers of mistreatment with antibiotics and antidiarrheals. In addition, future evaluations should be designed to assess these nuances, as well as the diarrhea treatment preferences and expectations of both providers and caregivers.

The results of the external evaluation of the DAZT program draw attention to factors of importance for future diarrhea management programs in Gujarat and UP, as well as generalizable areas throughout India and South Asia. An important conclusion of this evaluation is that the absence of demand generation activities targeting the community was a major flaw. The addition of activities aimed at generating demand for ORS and zinc among caregivers of young children would have complemented public and private sector activities. Community–level activities could have accelerated uptake of careseeking through ASHAs and AWWs, since lack of awareness of their ability to treat diarrhea was the leading reason reported at endline by caregivers who had never utilized ASHAs or AWWs for diarrhea care. Lack of diarrhea treatment supplies was an additional reason cited by caregivers who had never sought diarrhea treatment from ASHAs, AWWs or PHCs, thus underscoring the important link between preventing public sector ORS and zinc stock–outs and building trust among caregivers in the community. The results of the private sector evaluation demonstrate the potential role of private providers in provision of ORS and zinc despite the challenging nature of reaching informal providers; future programs may benefit from a systematic census to better characterize this population and facilitate coverage of the full universe of informal providers. Finally, our results suggest that provision of ORS and zinc are complementary in that the odds of receiving ORS increased with receipt of zinc and vice versa. This finding highlights the importance of emphasizing both ORS and zinc in training providers in either sector. Thus, as future diarrhea management programs are designed with the goal of introducing zinc, implementers must ensure that ORS is also given focus.

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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) and declare no conflict of interest.

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Adherence to zinc supplementation guidelines for the treatment of diarrhea among children under–five in Uttar Pradesh, India

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Laura Lamberti Johns Hopkins University Bloomberg School of Public Health Department of International Health 615 N. Wolfe Street Baltimore, MD 21205 Llamber3@jhu.edu **Background** There is limited evidence on adherence to the recommended dose and duration of zinc supplementation for diarrheal episodes in children under five years of age. In selected districts of Uttar Pradesh, India, we sought to assess adherence to the nationally advised zinc treatment regimen (ie, 10 mg/day for ages 2–6 months and 20 mg/day for ages 7–59 months for 14 days) among caregivers of zinc–prescribed children.

Methods We identified and conducted follow–up visits to children advised zinc for the treatment of diarrhea. At the initial visit, we collected data on the treatment instructions received from providers. Caregivers were asked to record treatments administered on a pictorial tracking form and were asked to retain all packaging for collection at follow–up. We quantified the average dose and duration of zinc therapy and built logistic regression models to assess the factors associated with caregiver adherence to national guidelines.

Results Caregivers administered zinc for an average of 10.7 days (standard deviation (SD) = 3.9 days; median = 13 days), and 47.8% continued treatment for the complete 14 days. Among children receiving zinc syrups and tablets respectively, the age appropriate dose was received by 30.8% and 67.3%. Adherence to age appropriate dose and continuation of zinc for 14 days were highly associated with having received appropriate provider instructions.

Conclusions Our results indicate moderate—to—good adherence to national zinc treatment guidelines for diarrhea among caregivers in rural India. Our findings also highlight the importance of provider guidance in ensuring adherence to zinc dose and duration. Programs aiming to scale—up zinc treatment for childhood diarrhea should train providers to successfully communicate dosing instructions to caregivers, while also addressing the tendency of caregivers to terminate treatment once a child appears to have recovered from an acute diarrheal episode.

The efficacy and effectiveness of therapeutic zinc supplementation in reducing the duration and severity of diarrhea among children under five years of age has been well–documented [1-3]. In response to mounting evidence, UNICEF and WHO revised the global childhood diarrhea treatment guidelines in 2004 to include continued feeding, low–osmolarity oral rehydration salts (ORS), and daily zinc supplementation for 10–14 PAPERS

days with 20 mg/d for children aged 6–59 months and 10 mg/d for infants aged <6 months [4]. Despite the global recommendation and the incorporation of zinc into the national diarrhea treatment policies of a growing number of countries, zinc treatment has failed to become available at scale over the past decade and attaining improved coverage of zinc, as well as ORS, has remained a challenge in most low– and middle–income countries [5].

In addition to concerns regarding access to zinc treatment for diarrhea among children under-five years of age, studies assessing adherence to the advised dose and duration of supplementation have called into question the quality of the regimen received by those actually treated with zinc [6-14]. A cluster randomized controlled trial (cRCT) in Bangladesh reported that on average children with diarrhea residing in intervention villages received only 7 days of the total 14-day zinc dosage [7]. In a study drawing evidence from cRCTs conducted in Brazil, Ethiopia, Egypt, Philippines and India (Nagpur and Lucknow), adherence to zinc for ≥10 days was 83.8% [6]. A cRCT conducted in Haryana, India found that in intervention villages the proportion of zinc-treated children receiving the full 14-day dose decreased from 70% to 61.9% when assessed at three and six months post-intervention, respectively [8]. These three studies highlight the challenges associated with achieving and maintaining high levels of zinc treatment adherence even under controlled research settings.

Evidence from observational studies suggests that in practice adherence to the zinc treatment guidelines may be less common among both providers and caregivers. In a 2005 evaluation of the Scaling up zinc for young children (SUZY) project, only 55.8% adhered to the advised 10-day duration of treatment, and the average zinc-treated child received zinc for 7-8 days in total [10]. In communities in Mali in which a zinc scale-up project was underway, adherence to 14 days of therapeutic zinc was 64% and though compliance with dosage instructions was generally good (94%), one infant received more than the age appropriate daily dose of zinc [14]. A cross-sectional study of caregivers of children under-five in Kenya reported low compliance with the guidelines on both zinc treatment duration (38%) and dosage (55%), with 32% of caregivers administering more than the age appropriate daily zinc dose [13].

Though there are limited studies assessing the issue of adherence to therapeutic zinc supplementation for diarrhea, the existing evidence highlights important research questions that should be addressed as the global community pushes toward the goal of scaling–up adequate diarrhea treatment. Evaluations of newly implemented diarrhea treatment programs should therefore be designed to not only gauge zinc coverage but also the level of adherence to the zinc treatment protocol among both providers and caregivers of children under–five. While coverage surveys capture the proportion of children with diarrhea who receive any course of zinc, it is possible that very minimal zinc treatment regimens do not confer the same benefits as the advised course. Therefore, the level of zinc adherence may affect the extent to which increases in coverage translate into impact on diarrhea morbidity and mortality outcomes in the long– term. Furthermore, monitoring adherence to zinc dosage instructions is important, since ingesting more than the age appropriate daily dose may pose a risk for zinc toxicity.

In an effort to address the question of zinc treatment adherence among caregivers of zinc-prescribed children under-five in rural India, we nested a sub-study within the external evaluation of the Diarrhea Alleviation through Zinc and ORS Treatment (DAZT) project in Uttar Pradesh (UP), India. To our knowledge, this is the first observational study to assess adherence to therapeutic zinc supplementation in rural India.

METHODS

Overview of the DAZT project and zinc adherence sub-study

The DAZT project was conducted in selected districts of UP from 2011–2014 with the goal of scaling–up ORS and zinc treatment of diarrhea among children 2–59 months of age. A complete description of the intervention and evaluation results are published elsewhere [15]. In brief, ORS and zinc supplies were made available to facility– and community–based public sector providers who also received thorough training in adequate treatment of childhood diarrhea. In the private sector, representatives of pharmaceutical companies were employed to solicit the sale of ORS and zinc to both qualified providers and informal, unlicensed providers.

The zinc adherence sub–study was designed to address the dearth of information on zinc treatment adherence among caregivers in rural India. Our main objective was three-fold: to estimate the proportion of caregivers who received zinc dose and duration instructions in agreement with national childhood diarrhea treatment guidelines; to estimate the proportion of caregivers that adhered to the course of zinc therapy advised by their child's provider; and to quantify the average zinc treatment dose and duration received by children in this population. The study was conducted from May through July, 2014 in the Lucknow and Mohanlal Ganj tehsils of Lucknow district and the Badaun and Bisauli tehsils of Badaun district in UP.

Sample size

In the absence of published estimates of zinc adherence in rural India, we employed the most conservative methodology and assumed the true proportion of adherent zinc– treated children to be 50%; this approach maximizes the sample size requirements and was the most appropriate given our limited knowledge on the outcome of interest in this population. We used Stata 12.0 statistical software to calculate the sample size required to generate a precision estimate of the point prevalence of adherent zinc-treated children within 10 percentage points with 95% confidence [16]. The resulting sample size requirement of 97 zinc-prescribed children was inflated to 120 to account for the possibility of loss-to-follow-up. We aimed to equally divide the required sample size of 120 zinc-prescribed children across the four included tehsils (ie, 30 per tehsil) but if interviewers encountered difficulty identifying zinc-prescribed children in a given tehsil due to unforeseen zinc treatment stock-outs or lower than anticipated prescribing practices, we allowed the sample size to be made up in the remaining tehsils.

Data collection

In each tehsil, we randomly selected 12 rural villages for inclusion in the study using probability proportional to size (PPS) sampling. Trained interviewers visited all households within the selected villages to identify children meeting the following inclusion criteria: 1) aged 2-59 months; 2) episode of diarrhea (defined as ≥ 3 loose or watery stools in a 24-hour period) in the 7 days preceding the household visit; 3) receipt of zinc treatment for diarrhea in the 3 days preceding the visit. To ensure the accuracy of zinc reporting, interviewers verified the third enrollment criterion by asking to see any available treatments or packaging from treatments administered to the child. If more than one child in the 2-59 month age range resided in the household, the primary caregiver was instructed to base her responses on the youngest. Consenting primary caregivers of zinc-treated children were formally interviewed regarding the place of zinc procurement, zinc treatment instructions received, and the dose/duration of treatment to date.

Interviewers scheduled follow-up visits for 14 days after the initial visit to all households in which a child met the inclusion criteria. The caregiver was asked to retain the packaging from any treatments administered to the child during this period and was also shown how to use a pictorial tracking form to record days on which the child experienced diarrhea and days on which the child was administered ORS and/or zinc syrup or tablets. The tracking form also included slots in which to record common daily activities (ie, feeding and bathing) such that dummy variables could be generated to assess caregivers' understanding of the tracking process. To reduce the threat of caregivers modifying their adherence behavior due to the scheduled follow-up visit, they were told that the purpose of the tracking form and visit was to check on the child's well-being following the diarrheal episode.

During the follow-up visit, the interviewer administered questions on the child's diarrheal episode and treatments given during the preceding 14 days and confirmed the caregiver's responses by referring to the tracking form and all reserved packaging. Interviewers also questioned caregivers regarding diarrhea treatment preferences, perceived benefits of zinc and reasons for discontinuing zinc treatment.

Statistical analyses

We conducted statistical data analyses using Stata 12.0 software [16]. We summarized the sociodemographic, diarrheal episode and zinc treatment characteristics of all children by calculating the means, standard deviations and medians of continuous variables and the proportions of categorical variables. We calculated the proportion of caregivers that received provider instructions on zinc dose and duration in agreement with the recommendation issued by the Government of India (GoI) and the Indian Academy of Pediatrics (IAP) (ie, 14 days supplementation with 10 mg/d for ages 2-6 months and 20 mg/d for ages 7-59 months) [17,18]; these guidelines differ slightly from WHO/UNICEF in the age cut-offs for dose but were the most appropriate gauge of adherence since DAZT project providers were trained according to the national protocol. We also calculated the proportion of caregivers that adhered to the provider-advised course of zinc therapy, the average duration of zinc treatment, and the proportion of children receiving an age appropriate dose. We conducted z-tests to assess the statistical equivalence of adherence by age category and zinc product formulation (ie, tablet or syrup).

We built three logistic regression models to assess the factors associated with adherence to the GoI/IAP advised dose and duration of zinc therapy with receipt of appropriate provider instructions as the primary explanatory variable. In each of the three models, respectively, we regressed: the log odds of continuing zinc for the complete 14 days onto an indicator of whether the provider advised zinc for 14 days (model 1); the log odds of receiving the age appropriate zinc dose onto an indicator of whether the provider gave such instructions (model 2); the log odds of receiving the age appropriate dose for 14 days onto an indicator of whether the provider advised the correct dose and duration of therapy. All models controlled for age category (7– 59 months vs 2-6 months), duration of the diarrheal episode in number of days, caregiver education (at least 1 year of school vs no school), and poor socioeconomic status as indicated by the possession of a BPL card (Table 1). To adjust for correlation in adherence behavior at the tehsil level, we employed the robust cluster estimator of variance in Stata 12.0 [16].

RESULTS

Follow–up visits were completed for 113 (94.2%) of the 120 caregivers of children meeting the inclusion criteria (**Figure 1**). The sociodemographic and diarrheal episode characteristics of these children are described in **Table 1**.

Details of zinc treatment

All caregivers were in possession of the zinc supplements used at the initial household visit. The majority of zinc was procured through the public sector (88.5%) and specifically from a community–based provider cadre known as Accredited Social Health Activists (ASHAs) (85.8%; **Table 2**). All product procured through the public sector was obtained free of charge, whereas private sector zinc product was purchased. Zinc sulfate was the most commonly used product (90.2%) and tablets were the most common formulation (89.3%; **Table 2**). All zinc products obtained from the public sector were in tablet form, and all but one zinc course procured from the private sector were syrups.

Reported zinc treatment instructions

Only a small proportion of caregivers (3.5%) received a zinc instructional pamphlet from the provider who advised treatment, but the majority reported receiving provider instructions on how to prepare and administer zinc (96.5%), on how long to continue the zinc treatment course (90.3%), and on the daily dose to administer (100%). On average, caregivers were advised to give zinc for 13.8 days (SD=1.2 days);

9695 households surveyed 4046 households with at least one child aged 2-59 months 340 caregivers unavailable (8.4%); 5 caregivers refuse consent (0.1%) Informed consent obtained from 3701 caregivers (91.5%) 658 caregivers report child with diarrhea in last 7 days (17.8%) 120 caregivers report child treated with zine in last 3 days (18.2%) 6 caregivers unavailable (5%); 1 caregiver refused visit (0.8%) Follow-up visits completed for 113 caregivers (94.2%)

Figure 1. Data collection profile.

Table 1. Sociodemographic and diarrheal episode characteristics of children with completed follow-up (n = 113)

	NUMBER (%)
Age of child (in months):	
Aged 2–6 months	23 (20.3)
Aged 7–59 months	90 (79.7)
Mean±SD	17.7±13.9
Median (range)	13 (2–59)
Sex:	
Male	48 (42.5)
Female	65 (57.5)
Episode characteristics:	
Blood in stool	13 (11.5)
Fever	83 (73.5)
Vomiting	40 (35.4)
Lethargic/irritable	84 (74.3)
Sunken eyes	54 (47.8)
Dehydration/Pani ki kami	71 (62.8)
Duration (days, mean±SD)	4.4 ± 3.0
Median (range)	3.0 (1–15)
Ethnic group:	
Scheduled caste	66 (58.4)
Scheduled tribe	2 (1.8)
Other backward castes	36 (31.9)
General	9 (8.0)
Caregiver years of schooling:	
Never attended school	44 (39.0)
Mean±SD	4.8 ± 4.5
Median (range)	5 (0–15)
Socioeconomic indicators:*	
Family possesses an APL card	47 (41.6)
Family possesses a BPL card	25 (22.1)
Family possesses an Antyodaya card†	13 (11.5)

SD – standard deviation, APL – above poverty line, BPL – below poverty line *Government of India–issued ration cards for subsidized food and fuel. †Antyodaya cards are issued to the poorest BPL families with income <250 rupees per month [18].

Table 2. Description of zinc product and place of procurement (n = 113)

	NUMBER (%)
Place of zinc procurement:*	
Public sector place of procurement:	100 (88.5)
- Accredited social health activist (ASHA)	97 (85.8)
– Anganwandi worker or center	3 (2.7)
Private sector place of procurement:	14 (12.4)
– Private provider	9 (8.0)
– Chemist	5 (4.4)
Zinc product:	
Zinc sulfate	102 (90.2)
Zinc acetate	8 (7.1)
Zinc gluconate	3 (2.7)
Zinc formulation:†	
Syrup	13 (11.5)
Tablets	101 (89.3)

*In one case, zinc was procured from both the public and private sectors. †In one case, zinc was obtained in both tablet and syrup formulations. All zinc products obtained via the public sector were in tablet form; all but one zinc product procured from the private sector was in syrup form. 89.4% were told to continue treatment for 10–14 days and 85.8% for exactly 14 days. Among children 2–6 months of age, appropriate dosage instructions (ie, 1/2 tablet/d or 5mL/d) were received by 65% and 33% of those treated with tablets and syrups, respectively. In the older age group, appropriate dosage instructions (ie, 1 tablet/d or 10mL/d) were received by 69% treated with tablets and 20% treated with syrups. In total, 55.8% (n=63) of caregivers were advised according to the GoI/IAP guidelines on both dose and duration of zinc treatment [17,18]. In addition to zinc, 76.1% (n=86) were also advised to administer ORS.

Reported zinc treatment adherence

On average, children received zinc for 10.7 days (SD = 3.9 days, median = 13 days). Zinc treatment was continued for 10–14 days and for the complete 14 days by 63.7% (n = 72) and 47.8% (n = 54) of caregivers, respectively. The age appropriate dose was administered to 30.8% of the 13 syrup–treated children and to 67.3% of the 101 tablet–treated children.

Of the 97 caregivers instructed by providers to continue zinc therapy for 14 days, 52.6% adhered. There was no statistically significant difference in adherence to the duration of treatment by the child's age (P=0.996). Adherence to the advised 14 days was higher among children treated with tablets (53.3%) compared to syrups (40.0%) but this difference was not statistically significant (P=0.563).

Adherence to dosage instructions was 87.5% among the 72 caregivers who received age appropriate advice; when stratified by age, 92.9% of caregivers of children <6months

were dose–adherent compared to 86.2% in the older age group (P=0.500). There was no statistically significant difference in adherence to age appropriate dosage instructions by product formulation of tablets (75.0%) compared to syrups (88.2%, P=0.437). No child received more than one zinc dose per day but, but 2 (20.0%) syrup–treated and 4 (66.7%) tablet–treated children aged 2–6 months received the daily dose intended for children in the older age category.

Of the 63 caregivers advised appropriately on both dose and duration, 46.0% (n=29) complied with both sets of instructions. All 86 caregivers told to administer ORS did so at least once during the episode.

Factors associated with zinc treatment adherence

Continuation of zinc treatment for 14 days and adherence to age appropriate dose were highly associated with appropriate provider instructions (**Table 3**). Controlling for age and other factors, the odds of continuing treatment for 14 days (adjusted odds ratio, aOR=6.43; 95% confidence interval (CI)=3.09–13.37) and of administering the correct dose for age (aOR=32.46, 95% CI 8.06–130.66) were elevated among caregivers instructed accordingly. In addition, the odds of adhering to the GoI/IAP guidelines on both dose and duration were higher among caregivers who received such advice from providers (aOR=9.97, 95% CI 4.10–24.25). Age category, episode duration, caregiver education and household BPL status were not associated with adherence to guidelines on dose and duration when assessed as separate outcomes (**Table 3**; **Models 1 and 2**),

Table 3. Factors associated with adherence to Government of India and the Indian Academy of Pediatrics guidelines on the dose and duration of zinc therapy for diarrhea*

	MODEL 1	MODEL 2	Model 3
Outcome	Zinc continued for 14 days Age appropriate zinc d		Age appropriate zinc dose for 14 days
	A	djusted odds ratio (95% confider	nce interval)
Appropriate provider instruction [†]	6.43 (3.09–13.37)‡	32.46 (8.06–130.66) ‡	9.97 (4.10–24.25) ‡
Child age:			
7–59 months	1.44 (0.65–3.18)	0.29 (0.03–2.54)	0.44 (0.22–0.87)§
2–6 months	1.0	1.0	1.0
Episode duration (days)	1.07 (0.99–1.14)	1.00 (0.82–1.22)	1.05 (0.92–1.21)
Caregiver education:			
≥1 year schooling	1.07 (0.77–1.50)	1.08 (0.47–2.47)	0.86 (0.50–1.48)
Never attended school	1.0	1.0	1.0
Household below poverty line¶	1.01 (0.39–2.58)	0.57 (0.24–1.39)	0.45 (0.22–0.92)§

*Government of India/India Academy of Pediatrics guidelines advise zinc supplementation for 14 days in the daily tablet/syrup dose of 10 mg/5mL for infants aged 2–6 months and 20 mg/10 mL for children aged 7–59 months.

†Model 1: provider advised zinc for 14 days; Model 2: provider advised zinc dose appropriate for child's age; Model 3: provider advised age appropriate dose to be continued for 14 days.

*Statistically significant: *P*<0.001.

§Statistically significant: P<0.05.

¶As indicated by possession of a Below Poverty Line card.

but adherence to both dose and duration was lower among caregivers of children aged 7–59 months (aOR=0.44, 95% CI 0.22–0.87) and those from households below the poverty line (aOR=0.45, 95% CI 0.22–0.92) (**Model 3**).

The majority of caregivers who failed to administer zinc for the full 14 days reported the child's recovery from diarrhea as the main reason for discontinuing zinc therapy (69.5%; **Table 4**). Commonly reported reasons also included administering another treatment (27.1%) and the perception that zinc was not working (17.0%). Running out of zinc product (5.1%) and the inability to afford zinc (3.4%) were mentioned by only a small proportion of caregivers, and concerns over vomiting or dislike of taste were not reported at all.

Caregiver perceptions of zinc treatment

Zinc was not frequently reported as the preferred treatment for childhood diarrhea (29.2%) compared to ORS (58.4%), syrups (81.4%) and tablets (92%). The perceived benefits of zinc among caregivers included reduced stool frequency (56.6%) and volume (5.3%), as well as decreased duration (18.6%) and severity (5.3%) (**Table 5**). Caregivers also re-

 Table 4. Reported reasons for shortened duration of treatment among caregivers who administered zinc for <14 days (n=59)</th>

	Number (%)
Reported reason zinc given for <14 days*	
Gave zinc for the advised number of days†	4 (6.8)
Child recovered	41 (69.5)
Child was given other treatment	16 (27.1)
Zinc was not working	10 (17.0)
Ran out of zinc supplies	3 (5.1)
Could not afford more zinc supplies	2 (3.4)
Child vomited	0
Child did not like taste of zinc	0

*Column totals exceed 59 as more than one reported reason was permitted. †Comparison of the advised duration of treatment as reported during the initial visit to the total number of days zinc was given as assessed at follow–up shows the 4 respondents who said they gave zinc for the recommended number of days actually continued treatment for less than the advised number of days.

Table 5. Reported benefits of zinc among enrolled caregivers	
(n=113)	

	Number (%)*
Reduces frequency of stool	64 (56.6)
Good for diarrhea/acts as drug for diarrhea	54 (47.8)
Makes child stronger/healthier	46 (40.7)
Treats/reduces risk of disease or illness	46 (40.7)
Reduces duration of diarrhea	21 (18.6)
Reduces severity of diarrhea	6 (5.3)
Reduces stool volume	6 (5.3)
Acts as a tonic after diarrhea	5 (4.4)
No benefit reported	18 (15.9)

*Column totals exceed 113 as more than one response was permitted.

ported that zinc is good for diarrhea (47.8%) and makes children healthier and stronger (40.7%). However, 15.9% of caregivers were unable to list any benefit of zinc.

DISCUSSION

Our study sheds light on provider and caregiver adherence to the national guidelines on zinc treatment for childhood diarrhea in rural India. The overall results are encouraging, illustrating moderate—to—good adherence to the GoI/IAP zinc therapy protocol by providers and to provider instructions by caregivers.

Among providers, the proportion advising continuation of zinc for 14 days (85.8%) was higher than that advising age appropriate dose (63.7%). In addition, a higher proportion of providers offered correct dosage instructions on tablets than syrups. We observed the opposite trend among caregivers for whom adherence to provider instructions on the 14-day duration of zinc treatment (52.6%) was lower than those on age appropriate dose (87.5%). This finding suggests that the zinc adherence challenges are different for providers and caregivers and thus critical to future program planning. Providers may experience difficulty in recalling and/or communicating zinc dose instructions, which are complicated by age cut-offs and differences by product formulation (ie, tablet vs syrup). On the other hand, caregivers are required to remember only one set of dosage instructions tailored to their child's specific age and product formulation and are perhaps less likely to encounter recall issues.

Our data indicate that for caregivers, compliance to dose is less challenging than continuation of zinc for the advised number of days, which is made difficult by the tendency to terminate treatment once a child appears to have recovered from diarrhea. Since the majority of diarrheal episodes among children under-five are acute (ie, typically 3-7 days), there is considerable discordance between the duration of illness and the advised therapeutic course. In a recently published RCT, the majority of participants (73.7%) could not be included in per-protocol analyses because treatment of both placebo- and zinc-randomized children was discontinued when diarrhea halted [9]. In order to increase the proportion of children receiving the full zinc treatment regimen, future programs must address the inclination of caregivers to terminate treatment once a child appears to have recovered. To this end, messages disseminated in the community should emphasize the general health benefits of zinc that extend beyond diarrhea treatment. In addition, it is important that providers are trained to not only counsel caregivers on the appropriate duration of supplementation but to also explain the rationale for continuing zinc after diarrheal symptoms have subsided.

Formative research should be conducted to identify salient messages that promote the use of zinc during both diarrhea and convalescence [6,19]. These strategies should succeed in increasing the proportions of caregivers who prefer zinc for diarrhea treatment and perceive zinc as beneficial to a child's overall health.

We observed a strong correlation between receipt of proper zinc treatment instructions and the odds a child received the age appropriate dose for 14 days. This finding is critical as it underscores the willingness of caregivers to heed the diarrhea treatment advice of providers and thus the importance of ensuring providers are well-trained. We did not find any evidence of children receiving more than one zinc dose per day, but six infants 2-6 months of age received the dose intended for older children. Future diarrhea treatment programs should ensure adequate training of providers in the complex zinc dosage guidelines, especially for young infants. Providers might benefit from visual demonstrations and hands-on practice in the preparation of each of the four zinc syrup/tablet doses. This approach could potentially maximize providers' retention of age cut-offs and ability to communicate such information to caregivers.

Our findings confirm reports that zinc treatment does not interfere with adherence to ORS [6,8], as all caregivers who reported being instructed to administer ORS complied. Future programs should continue simultaneous scale–up of ORS and zinc in rural India. Moreover, provider trainings should emphasize the importance of advising both products while program implementers concentrate on ensuring supply chain sustainability and prevention of stock–outs.

This study is limited by the reliance on caregiver report to gauge provider instructions on zinc treatment dose and duration. We reduced the threat of recall bias among caregivers by restricting inclusion to children with diarrhea occurring in the last 7 days who were treated with zinc in the 3 days preceding the initial household visit. Possession of zinc products and packaging among all enrolled caregivers at the first household visit suggests that zinc procurement and thus receipt of zinc instructions occurred recently relative to the timing of the visit, thereby lessening the likelihood of misreporting. To prevent recall issues at follow–up, we employed tracking forms to assist caregivers in monitoring treatment of the episode.

This study is also limited by an inability to stratify estimates of adherence by the sector or specific provider cadre from which zinc was procured, since the overwhelming majority of zinc was advised by ASHAs (85.8%). This limitation highlights larger programmatic questions concerning the limited availability of zinc stocks and the low propensity to advise zinc treatment in the private–sector and through certain public–sector outlets [15]. Nonetheless, our findings add to the evidence base on zinc adherence and suggest that among children prescribed zinc within select DAZT program areas, the quality of zinc treatment is generally high albeit with room for improvement.

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Ethical approval: We received ethical approvals from the Johns Hopkins School of Public Health Institutional Review Board and the Society for Applied Studies Ethical Review Committee. All survey and consent forms were translated from English to Hindi and back–translated to ensure accuracy. Trained data collectors obtained informed consent from caregivers before administering screening questions to ascertain whether the child met the study's inclusion criteria. The informed consent procedures consisted of reading the consent document aloud and obtaining a signature or, for illiterate caregivers, a fingerprint in the presence of a witness. All consenting caregivers were provided with a copy of the consent form and a list of phone numbers for local study contacts who could address questions and concerns.

Authorship declaration: LML designed the study, conducted the analyses and led the manuscript preparation. ST and SM designed the study, oversaw data collection and contributed to the manuscript. CFW and REB designed the study and contributed to the analyses and manuscript preparation.

Competing interests: All authors have completed the Unified Competing Interest form at www.ic-mje.org/coi_disclosure.pdf (available on request from the corresponding author). The authors report no conflict of interest.

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Birth prevalence of selected external structural birth defects at four hospitals in Dar es Salaam, Tanzania, 2011–2012

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Rogath Saika Kishimba PO Box 77784 Dar es Salaam Tanzania rogatkishimba@yahoo.ca **Background** 94% of all birth defects (BD) and 95% of deaths due to the BD occur in low and middle income countries, many of which are preventable. In Tanzania, there is currently a paucity of BD data necessary to develop data informed prevention activities.

Methods A cross-sectional analysis was conducted of deliveries identified with BD in the labor ward registers at four Dar es Salaam hospitals between October, 2011 and February, 2012. The birth prevalence of structural BD, case fatality proportion, and the distribution of structural defects associated deaths within total deaths were calculated.

Results A total of 28217 resident births were encountered during the study period. Overall birth prevalence of selected defects was 28.3/10000 live births. Neural tube defects and indeterminate sex were the most and least common defects at birth (9.9 and 1.1/10000 live births, respectively). Among stillbirths (66.7%) and deaths that occurred within less than 5 days of an affected live birth (18.5%), neural tube defects were the most frequently associated structural defect.

Conclusion Structural BD is common and contributes to perinatal mortality in Dar es Salaam. More than half of perinatal deaths encountered among the studied selected external structural BD are associated with neural tube defects, a birth defect with well–established evidence based prevention interventions. By establishing a population–based BD surveillance program, Tanzania would have the information about neural tube defects and other major structural BD needed to develop and monitor prevention activities.

A birth defect is an abnormality of structure or function which originates during intrauterine life and is evident before birth, at birth or manifests later in life [1]. Major structural birth defects are present at birth and they typically have significant medical or surgical consequences. They arise from genetic or environmental causes, some are multifactorial, having both genetic and environmental causes, and for others the causes are still unknown [1]. Birth defects may be mild or severe. Major structural birth defects include congenital heart disease (CHD), neural tube defects (NTDs), orofacial clefts, and limb reduction defects; these defects are considered severe, having adverse effects on the well-being and survival of children born with those anomalies [1, 2]. Almost all birth defects (94%) and deaths due to the birth defects among children (95%) occur in low and middle income countries [2]. The global mortality associated with birth defects, as reported by the March of Dimes (MOD) is estimated at 3.3 million children under age five years dying from serious birth defects. Of those children who survive, it is estimated that 3.2 million may be disabled for life, without appropriate care. Birth defects exact a severe human and economic toll on those affected, their families and their communities [2,3].

In Tanzania, it is estimated that the prevalence of birth defects is 60.5 per 1000 live births [2]. Studies done at Muhimbili National Hospital neonatal unit in Dar es Salaam have shown a birth defects prevalence of 33 per 1000 live births, and a prevalence of 3.0 per 1000 live births for NTDs [4,5]. Eight percent of the overall neonatal mortality was attributed to birth defects [5]. There remains a paucity of data in Tanzania on birth defects. This is due to constrained diagnostic capabilities, lack of awareness of available services, and the absence of a birth defects surveillance system and registry. The absence of routine, reliable and systematically collected data prevents the development of information necessary to develop, monitor, and evaluate prevention strategies. This study establishes the magnitude of selected major structural defects in Dar es Salaam, Tanzania and characterizes the burden, providing evidence for the usefulness of a birth defects surveillance system, including the development of data informed birth defects prevention activities.

METHODS

This study included all newborns delivered from October, 2011 through February, 2012 in Dar es Salaam from Muhimbili National Hospital (MNH) and all three Municipal hospitals (Temeke, Mwananyamala and Amana). Ninety percent of births to Dar es Salaam residents occur in a health facility, and 72% of Dar es Salaam residents deliver at Muhimbili National Hospital or at one of the three municipal hospitals [6,7]. These hospitals are the biggest public hospitals in Dar es Salaam, serving populations with diverse ethnic and demographic characteristics as well as health related behaviors. None of the municipal hospitals are referral hospitals for mothers with a prenatal diagnosis of a fetus with birth defects as this is not in our standard Reproductive and Child Health Antenatal Recommendation, and termination of pregnancies for fetal anomalies are not allowed.

A case was defined as any live birth or stillbirth identified at delivery with a selected external major birth defect in any of the four hospitals during the study period. Study data came from a review and abstraction of labor ward registers during the study period (October 2011 to February 2012). Data were abstracted daily by trained midwives. Labor ward admission and discharge procedures were similar in all study sites. Every pregnant woman who was in labor pain was admitted and registered. Her particulars like name, age, place of residence, gravity and parity are recorded. After giving birth, a complete clinical evaluation of the infant is done by the Medical Officer and if he/she had any medical problem including birth defects, he/she is sent to the neonatal unit for further care and treatment. If he/she has no problem, the baby is given to his/her mother, which will stay at least 24 hours before being discharged.

The international classification of diseases version 10 (ICD10) was used to code selected external major structural defects [8]. The selected structural defects were further classified as having only one major birth defect (isolated), having more than one major birth defect (multiple) or occurring as part of a genetic or chromosomal condition (syndrome). All newborns delivered during the study period to Dar es Salaam resident mothers (women who lived in Dar es Salaam for the 6 months prior to delivery) were included in this study. A standard data collection form was developed and used to collect maternal, paternal, and newborn demographic data. The form included collecting the patient registration number to avoid duplication of cases, along with the name of the delivery hospital, date of birth, sex of the newborn, and type of birth defect.

Data were entered, cleaned, and analyzed using Epi Info Version 3.5.1. (Centers for Disease Control and Prevention, Atlanta, GA, USA). The birth prevalence of selected major structural defects was calculated by dividing the total number of newborns (live and stillbirths) with selected structural defects (central nervous system defects, orofacial clefts, congenital malformations of the genital organs, musculoskeletal defects, and chromosomal abnormalities) delivered during the study period (Numerator) by the total number of live births delivered at participating hospitals during the same time period (Denominator) [9]. The distribution of deaths within defect types was calculated by dividing the number of deaths associated with a specific defect by the total number of deliveries affected by that specific defect (live births + still births), multiplied by 100. This was calculated separately for live births that survived less than 5 days and stillbirths. The distribution of selected structural defects associated deaths within total deaths was calculated by dividing the number of defect specific deaths by the total number of defect associated deaths. This was calculated separately for live births that survived less than 5 days and stillbirths.

The protocol for this study was approved by the Internal Review Board of Muhimbili University of Health and Allied Sciences (MU/PGS/SAEC/Vol.VI/2011) and Muhimbili National Hospital (No. 150 2011/2012). Names of respondents were not recorded in the data collection form and measures were taken to ensure confidentiality and security of the information collected.

RESULTS

During the study period, a total of 28217 deliveries occurred in the four participating hospitals of which 27230 were live births. Seventy seven newborns (28.3 per 10000 live births) had one of the selected external major structural defects. Of the 77 newborns with selected structural defects, 38 (49.3%) were males, 36 (46.8%) females and 3 (3.9%) had undetermined sex (Table 1). When considering all deliveries in the denominator, the birth prevalence of selected structural defects is similar to when only live births are included in the denominator for calculating birth prevalence (27.3 per 10000 total births). Males and females had a similar overall birth prevalence of selected structural defects, though NTDs were more common among females, and isolated hydrocephalus and orofacial defects were more common among males. Neural tube defects had the highest overall birth prevalence (9.9/10000 live births) among the selected external major structural defects. Indeterminate sex defects and chromosomal abnormalities had the lowest overall birth prevalence among the selected structural defects, respectively (1.0/10 000 live births and 1.8 /10 000 live births).

The majority of selected external structural defects were isolated (74%), while19.5% had multiple anomalies and 6.5% had syndromes. Overall, 76.6% of deliveries (live births + stillbirths) with selected external structural defects survived at least 5 days, with 15.6% dying prior to delivery (stillbirth), and 7.8% dying within 5 days of delivery (**Table 2**). Neural tube defects had the highest defect–specific mortality among live births and total deliveries (live births + stillbirths) and represented the majority of stillbirths and under 5–day deaths among selected structural defect–affected pregnancies.

DISCUSSION

In the diverse birth population of Dar es Salaam, we observed that NTDs, one of the selected external structural defects with the greatest opportunity for prevention, were the most prevalent structural defect followed by musculoskeletal defects. This finding is in contrast to other studies conducted in different parts of the world – Uganda, Nigeria, South Africa and Israel– where musculoskeletal defects were the most common birth defects [10–14]. This may be due to our study's focus on just two major birth defects of the musculoskeletal system. Our observation that NTD birth prevalence was slightly higher in female newborns than males is similar to a study done in Iran whereby they observed two thirds of NTD–affected newborns were fe-

Table 1. Birth prevalence of selected major structural birth defects, by sex, Muhimbili National Hospital and three Municipal hospitalsin Dar es Salaam, Tanzania, 2011–2012

Birth defect	ICD 10	Live births and fetuses with birth defects (Count (n), prevalence per 10 000 live births (P); 95% Confidence interval (CI) (95%)			
		Male	Female	Undetermined	Total
		N=13550	N = 13677	N=3	N=27230
CNS defects	-	$n = 18 \ (P = 13.3)$	n=21 (15.4)	-	n=39 (P=14.3; 95% CI=10.2–19.6)
Neural tube defects:	_	n = 10 (P = 7.4)	n = 17 (P = 12.4)	_	n=27 (P=9.9; 95% CI=6.5–14.4)
Anencephaly	Q00.0	n = 5 (P = 3.7)	n = 9 (P = 6.6)	-	n=14 (P=5.1;95% CI=2.8-8.6)
Spina bifida	Q05	n = 5 (P = 3.7)	n = 5 (P = 3.7)	-	n=10 (P=3.7; 95% CI=1.8–6.6)
Encephalocele	Q01	$n = 0 \ (P = 0.0)$	n=3 (P=2.2)	-	n=3 (P=1.1; 95% CI=0.2-3.2)
Isolated hydrocephalus	Q03	n=8 (P=5.9)	n = 4 (P = 2.9)	_	n=12 (P=4.4; 95% CI=2.3–7.7)
Orofacial clefts:	_	n = 7 (P = 5.2)	n = 4 (P = 2.9)	_	n=11 (P=4.0; 95% CI=2.0–7.2)
Cleft palate	Q35	n=2 (P=1.5)	n = 1 (P = 0.7)	_	n=3 (P=1.1; 95% CI=0.2–3.2)
Cleft lip	Q36	n=3 (P=2.2)	n = 1 (P = 0.7)	-	n=4 (P=1.5; 95% CI=0.4-3.8)
Cleft palate with cleft lip	Q37	n=2 (P=1.5)	n=2 (P=1.5)	-	n=4 (P=1.5; 95% CI=0.4-3.8)
Indeterminate sex	Q56	_	-	n=3 (P=1.5)	n=3 (P=1.1;95% CI=0.2–3.2)
Musculoskeletal defects:		n = 10 (P = 7.4)	n = 9 (P = 6.6)	_	n=19 (P=7.0;95% CI=4.2–10.9)
Talipes equinovarus	Q66.0	n = 8 (P = 5.9)	n = 7 (P = 5.1)	-	n=15 (P=5.5; 95% CI=3.1–9.1)
Reduction defects of upper and lower limbs	Q71 & Q72	n=2 (P=1.5)	n=2 (P=1.5)	_	n=4 (P=1.5; 95% CI=0.4–3.8)
Chromosomal abnormalities:	-	n=3 (P=2.2)	n=2 (P=1.5)	-	n=5 (P=1.8; 95% CI=0.6–4.3)
Down syndrome	Q90.9	$n = 1 \ (P = 0.7)$	n=2 (P=1.5)	-	n=3 (P=1.1; 95% CI=0.2–3.2)
Edward syndrome	Q91.3	n=2 (P=1.5)	-	-	n=2 (P=0.7; 95% CI=0.1–2.7)
Total	-	n = 38 (P = 28.0)	n = 36 (P = 26.3)	n=3 (P=1.0)	n=77 (P=28.3; 95% CI=22.3–35.3)

Survived \geq 5 days	Survi	Survived <5 days Stillbirth			TOTAL		
No.	No.	% within specific defects	% within live births	No.	% within specific defects	% within still- births	No.
14	5	18.5	83.3	8	29.6	66.7	27
9	1	8.3	16.7	2	16.7	16.7	12
10	0	0	0	1	9.1	8.3	11
2	0	0	0	1	33.3	8.3	3
19	0	0	0	0	0	0	19
5	0	0	0	0	0	0	5
59	6	7.8	100	12	15.6	100	77
	No. 14 9 10 2 19 5	No. No. 14 5 9 1 10 0 2 0 19 0 5 0	specific defects 14 5 18.5 9 1 8.3 10 0 0 2 0 0 19 0 0 5 0 0	No. No. % within specific defects % within live births 14 5 18.5 83.3 9 1 8.3 16.7 10 0 0 0 2 0 0 0 19 0 0 0 5 0 0 0	No. No. % within specific defects % within live biths No. 14 5 18.5 83.3 8 9 1 8.3 16.7 2 10 0 0 0 1 2 0 0 0 1 19 0 0 0 0 1 5 0 0 0 0 0	No. % within specific defects % within live births No. % within specific defects 14 5 18.5 83.3 8 29.6 9 1 8.3 16.7 2 16.7 10 0 0 0 1 9.1 2 0 0 0 1 33.3 19 0 0 0 0 0 5 0 0 0 0 0 0	No. No. % within specific defects % within live births No. % within specific defects % within specific births 14 5 18.5 83.3 8 29.6 66.7 9 1 8.3 16.7 2 16.7 16.7 10 0 0 0 1 9.1 8.3 2 0 0 0 1 33.3 8.3 19 0 0 0 0 0 0 0 5 0 0 0 0 0 0 0 0 0

Table 2. Counts, distribution of deaths within specific defects, and distribution of deaths within live births and stillbirths, National hospital and three Municipal hospitals in Dar es Salaam, Tanzania, 2011–2012

male [15]. However findings from studies conducted in Nigeria were in contrast to our observation [16,17]. The difference may relate to differences in the distribution of specific NTD types between the populations, as we observed the difference was driven by two of the three major NTD types. In our study, the birth prevalence of anencephaly was higher than that of spina bifida; this finding was comparable to studies done in Yaoundé Cameron and Texas, United States which observed a higher prevalence of anencephaly than spina bifida [18,19]. Neural tube defects prevalence was comparable to the prevalence reported by India to the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) [20].

We did not identify a significant birth defect prevalence difference when considering only live births and total deliveries as denominators. Isolated birth defects were more common than multiple and syndrome birth defects, a finding similar to a prospective neurosurgical observational study done in Nigeria to assess central nervous system congenital anomalies [16]. Among NTD-affected newborns the percentage who were stillborn and who were alive for less than 5-days was higher than for other selected external structural defects. This likely reflects that NTDs are the most serious and fatal birth defects compared to the other defects included in this study as has been previously reported [21,22]. A study done in the United Kingdom among male radiation workers at the Sellafield nuclear processing plant showed that risk of stillbirth among their offspring was highest among NTD-affected fetuses [23]. In a hospital based epidemiological descriptive study done in Iran that reviewed live births and stillbirths for a period of 4.5 years, showed a prevalence rate of NTDs among stillbirths being more than twice that among live births [15].

Evidence shows that preconceptional use of folic acid helps prevent NTDs, and many countries are implementing mandatory fortification of folic acid in cereals [24–28]. In the United States folic acid fortification resulted in an approximate 19% decrease in the incidence of NTDs [24]. Folic acid supplementation, through the consumption of vitamins, is an alternative approach to fortification that has been shown to reduce the primary incidence of NTD by 62% and recurrence of NTD by 70% [28]. In developed countries, folic acid supplementation policy faces significant challenges from unplanned pregnancies, lack of easy access to a functioning health system and effective local social marketing interventions [29-31]. In developing countries like Tanzania, folic acid supplementation policy will be difficult to implement given that these countries have high levels of poverty, poor health care infrastructure, and high rates of unplanned pregnancies compared to their counterparts [32-34]. Mandatory folic acid fortification policy is an option for developing countries to consider, which overcomes some of the challenges of supplementation. Tanzania is currently implementing a mandatory large scale wheat flour fortification policy. Having a birth defects surveillance system in place will help facilitate monitor this prevention strategy, and will help identify populations at risk in need of targeted interventions.

Interpretation of these study findings need to be considered in relation to several strengths and weaknesses. One of the major strengths of this study is that all births were thoroughly evaluated during the study period by clinical professionals. This made it possible to capture birth defects among stillbirths or births that survived less than 5 days, which would not have been possible if our study ascertained birth defects by either retrospective review of data from neonatal units or collecting data from either neonatal admission units or birth defects clinics alone. These alternative approaches would have resulted in underestimating the burden of structural birth defects included in this study. An additional strength of this study is the involvement of multiple public hospitals, representing the majority of deliveries to Dar es Salaam residents and covering people with a diversity of demographic characteristics and health related behaviors.

CONCLUSION

This study was limited by the duration of follow-up. New-

borns with structural birth defects were followed up for

only 5-days, and so the contribution of the selected struc-

tural defects to early mortality is a likely underestimate,

though there is no evidence that the distribution of select-

ed defects among deaths would differ at 2-weeks or 1-

month after delivery. Also only selected major external

birth defects were included during the study period to fa-

cilitate identification and avoid under reporting. Internal

major birth defects were not included due to limitations in

technology to diagnose them. Another limitation of this study was that it only included hospital deliveries, which

could have either led to underestimation or overestimation

of birth prevalence; however, 90.2% of births to Dar es Sa-

laam residents occur in health facilities [6]. Our study was

facility-based, and so generalizability of the findings are

limited to births in the study facilities; however, deliveries

at these facilities represent 72% of all deliveries in Dar es

This study demonstrates that structural external major birth defects are frequent in clinical practice in Dar es Salaam. NTDs were the most common occurring, followed by musculoskeletal defects and orofacial clefts. The majority of stillbirths with selected external structural defects were associated with a neural tube defect which has a well–established evidence based prevention interventions. We can therefore lower perinatal mortality through preventing neural tube defects particularly spina bifida and anencephaly.

By establishing a population based birth defects surveillance program, which can provide accurate and reliable estimates of the prevalence and risk factors for NTDs and other major birth defects, Tanzania will have the information necessary for the effective development and monitoring of birth defects prevention activities, including folic acid fortification.

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Authorship declaration: RK, RM, JMM and DG designed the study. RK, RM and JMM conducted the study, including newborns recruitment, data collection, and data analysis. RK prepared the manuscript draft with important intellectual input from DV, RM, JMM and DG. All authors approved the final manuscript. RK had complete access to the study data.

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Assessment of Malawi's success in child mortality reduction through the lens of the Catalytic Initiative Integrated Health Systems Strengthening programme: Retrospective evaluation

(i)

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Prof Tanya Doherty Health Systems Research Unit, South African Medical Research Council Francie van Zijl Drive, Parow, Cape Town, 7535 South Africa tanya.doherty@mrc.ac.za **Background** Malawi is estimated to have achieved its Millennium Development Goal (MDG) 4 target. This paper explores factors influencing progress in child survival in Malawi including coverage of interventions and the role of key national policies.

Methods We performed a retrospective evaluation of the Catalytic Initiative (CI) programme of support (2007–2013). We developed estimates of child mortality using four population household surveys undertaken between 2000 and 2010. We recalculated coverage indicators for high impact child health interventions and documented child health programmes and policies. The Lives Saved Tool (LiST) was used to estimate child lives saved in 2013.

Results The mortality rate in children under 5 years decreased rapidly in the 10 CI districts from 219 deaths per 1000 live births (95% confidence interval (CI) 189 to 249) in the period 1991–1995 to 119 deaths (95% CI 105 to 132) in the period 2006–2010. Coverage for all indicators except vitamin A supplementation increased in the 10 CI districts across the time period 2000 to 2013. The LiST analysis estimates that there were 10800 child deaths averted in the 10 CI districts in 2013, primarily attributable to the introduction of the pneumococcal vaccine (24%) and increased household coverage of insecticide–treated bednets (19%). These improvements have taken place within a context of investment in child health policies and scale up of integrated community case management of childhood illnesses.

Conclusions Malawi provides a strong example for countries in sub– Saharan Africa of how high impact child health interventions implemented within a decentralised health system with an established community–based delivery platform, can lead to significant reductions in child mortality.

Since 2010, Malawi has been on track to reach Millennium Development Goal (MDG) 4 and is one of the first countries in sub–Saharan Africa to have reached the target [1], despite reporting one of the lowest gross national incomes per capita in the world [2]. According to the UN Inter– Agency Group for Child Mortality Estimation, under–5 mortality has declined steadily from 245 to 68 deaths per 1000 live births between 1990 and 2013 [3]. Malawi showed commitment to accelerating child survival and development through the establishment of the Accelerated Child Survival and Development policy in 2006 which was implemented through the Integrated Management of Childhood Illness (IMCI) five year strategic plan (2006–2011) and the Strategic Plan for Child Survival in 2007. The strategy aimed to reduce childhood morbidity and mortality by two–thirds between 2000 and 2015, and it focused on the scaling up of high impact interventions including integrated community case management of childhood illnesses and newborn care (iCCM) [4].

From 2008 iCCM was scaled up nationally under the coordination of the Ministry of Health with the support of partners in different districts including UNICEF, WHO, Save the Children, and others. UNICEF worked as an implementing partner in ten of twenty–eight districts throughout the country through the Catalytic Initiative (CI) Inte-

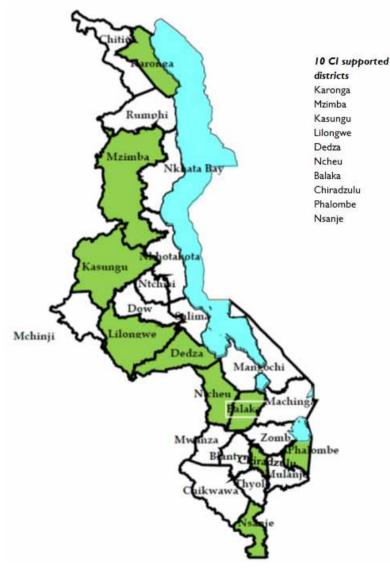


Figure 1. Map of Malawi showing 10 Catalytic Initiative districts (shaded in green).

grated Health Systems Strengthening (IHSS) programme (**Figure 1**) whilst other partners provided similar support in the remainder of the country. In 2013, an estimated 41 000 under–5 deaths occurred nationally with approximately 47% in the ten CI focus districts [3].

The CI/IHSS programme was established by UNICEF with joint funding from the Department of Foreign Affairs, Trade and Development Canada (DFATD) in late 2007 with the main aim of assisting low and middle–income countries in Central, West and Southern Africa with high maternal and child mortality rates, including Malawi, to scale up services to children and pregnant women [5]. The CI programme had a strong health systems strengthening focus through training of front line health workers, provision of drugs and supplies, support for supervision and development of monitoring and evaluation systems [6]. In the initial period the CI programme in Malawi supported mainly preventive

interventions including provision of vitamin A supplementation, immunisations, counselling on infant and young child feeding as well as training almost 4000 nurses in Integrated Management of Childhood Illnesses (IMCI). Following the Ministry of Health decision to scale up iCCM, the focus was on training and equipping of community health workers called health surveillance assistants (HSAs) to deliver iCCM services for treatment of malaria, pneumonia and diarrhoea [7]. As one of six countries participating in the CI programme, Malawi received a total of US\$ 19.4 million from DFATD (US\$ 11.5) and UNICEF (US\$ 7.9) over the grant period 2007–2013 [8].

HSAs have played a central role in the delivery of health services in Malawi since the 1960s, delivering an increasingly broad array of services at the community level [9–11]. Initially operating as environmental health outreach assistants concentrating on water and sanitation; since 1995 HSAs have been formally recruited and salaried by the Ministry of Health. Required to have grade 10 (junior certificate of education) to qualify, HSAs receive 12 weeks of general training, and since 2008, an additional 6 days of specific training on iCCM. They split their working week between the village clinic (situated in hard-toreach areas >5km from the nearest health centre) in which they spend 2-3 days per week, community-based outreach work and assisting in fixed health facilities. In 2011 there were over 10000 HSAs in the country of which 3800 had been trained in iCCM with just over 1000 of these situated in the 10 districts where CI efforts

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were focused (**Figure 1**) [10]. Small–scale evaluations during the early period of iCCM implementation (2009–2011) revealed high demand for HSA services [10] and quality of care similar to that provided by nurses in first–level facilities [12]. An evaluation of changes in newborn survival identified areas for further work, including the integration of neonatal sepsis management into iCCM [13]. However, no evaluation has assessed the broader impact of child survival strategies, particularly iCCM, on child health indicators in Malawi. This paper explores factors influencing progress in child survival including coverage of interventions, the role of key national policies and impact of coverage change on under–5 deaths averted using data from an evaluation of the CI programme of support in Malawi.

METHODS

Study design and setting

The analyses undertaken were part of a multi–country retrospective evaluation of the CI programme. The selection of the 10 CI districts for UNICEF support was undertaken jointly by UNICEF and the Ministry of Health (**Figure 1**). The selected districts reported higher rates of maternal, newborn and child mortality in 2006 [14] compared to national mortality and included remote areas with limited health care access. The CI grant supported both facility and community–based interventions including preventive and curative services (**Box 1**). This evaluation compared average annual change (AAC) in coverage for key indicators in the 10 CI districts before the CI support began (2000–2006) and during the period of implementation (2007–2013).

Data sources

We used birth and death history data collected from women aged 15 to 49 years in nationally representative surveys: namely the 2000 Demographic and Health Survey (DHS), 2004 DHS, 2006 Multiple Indicator Cluster Survey (MICS), and the 2010 DHS to calculate under–5 mortality. The surveys covered 14213, 13664, 30553, and 24825 households respectively.

For analysis of intervention coverage we used standard indicator definitions [15] for 11 interventions targeted by the CI for tracking progress towards MDG 4 (**Table 1**). We also captured coverage change for other maternal and contextual indicators. Surveys included in the analysis of intervention coverage were the 2000 DHS, 2006 MICS, 2010 DHS and the 2013 Lot Quality Assurance Survey (LQAS) which sampled in the 10 CI districts only [16,17]. The 2004 DHS did not include disaggregated data for all of the CI districts; therefore it was excluded from the coverage analysis (Section A in **Online Supplementary Document**). All surveys provided cross–sectional data on intervention coverage in their respective years. Full survey data sets with **Box 1.** Interventions supported in Malawi through the Catalytic Initiative funding

Expanded Programme on Immunisation:

- Catch up immunisation through child health days
- Vitamin A supplementation

Health system strengthening of the health surveillance assistant (HAS) platform (particularly related to integrated community case management (iCCM) of malaria, pneumonia and diarrhoea):

- Communication and social mobilisation on iCCM (through job aids)
- Recruitment, selection and training of HSAs
- Basic supplies for HSAs (drug box, bicycles, motorcycles for supervision)
- Supervision (quarterly mentorship and review meetings on iCCM)
- M&E (support to M&E officer at IMCI unit)
- Review of health surveillance curriculae to include new competencies

Renovation of three training centers:

• Purchased sachets of oral rehydration salts (ORS) and zinc tablets, cotrimoxazole, sulfadoxine–pyrimethamine and artemisinin–combination therapies (ACTs) for village clinics

Integrated Management of Childhood Illnesses (IMCI):

• Training of nurses and clinicians in IMCI

Malaria prevention:

• Supply and distribution of ITNs for pregnant women and children under five years

Health promotion

Infant and young child feeding:

- Promotion of early initiation and exclusive breastfeeding for six months
- Screening for severe and acute malnutrition

WASH:

• Education on safe water, sanitation and hygiene

district sampling weights were used for the analysis. For further details on the surveys included in the analysis see Table s1 in **Online Supplementary Document**. Adjustments were made to align indicator definitions across the DHS, MICS and LQAS surveys (Section B in **Online Supplementary Document**).

Contextual information about child health policies, CI implementation and other relevant child health programmes was obtained through a desk review of documents and databases obtained during a 10–day country visit (August 2013). The information gathered from these sources was used to compile a policy and programme timeline (**Figure 2**). For further details on the contextual analysis see Panel s1 in **Online Supplementary Document**.

Table 1. Summary of indicator coverage change in the 10 Catalytic Initiative-focus districts

Indicator	DHS 2000 (pre–Cl) % (95% Cl)	MALAWI (10 CI DISTRICTS) MICS 2006 (baseline) % (95% CI)	LQAS 2013 (endline) % (95% CI)	Average annual change pre-CI (2000-2006: period 1; % per year with confidence	Average annual change during CI (2006–2013: period 2; % per year with confidence intervals)	Direction of change between period 1 and
Tetanus toxoid vaccination of pregnant women (at least 2 doses)	, ,	72 (70 to 74)	(99 % C1) 72 (69 to 75)	INTERVALS) 3.6 (3.1 to 4.1)	0.0 (N/A)	period 2‡ ↓
ІРТр	28 (26 to 31)	48 (46 to 51)	84 (82 to 87)	8.9 (8.1 to 9.8)	7.9 (7.5 to 8.4)	\rightarrow
Early breastfeeding	68 (66 to 71)	53 (51 to 56)	75 (72 to 79)	-4.1 (-4.6 to -0.2)	5.0 (4.4 to 5.6)	\uparrow
Exclusive breastfeeding	38 (33 to 43)	55 (50 to 60)	61 (57 to 64)	6.1 (4.8 to 7.5)	1.5 (0.5 to 2.4)	\downarrow
Vitamin A supplementation*	79 (76 to 82)	75 (71 to 78)	56 (52 to 59)	-0.8 (-1.1 to -0.6)	-4.2 (-4.9 to -3.4)	\downarrow
Measles immunisation	80 (77 to 84)	81 (78 to 84)	87 (84 to 89)	0.2 (to 0.2 to 0.6)	1.0 (0.6 to 1.4)	\uparrow
DPT3 immunisation	82 (79 to 85)	86 (83 to 88)	88 (86 to 91)	0.8 (0.4 to 1.2)	0.3 (0.0 to 0.7)	\rightarrow
Care-seeking of suspected pneumonia	26 (23 to 29)	52 (46 to 58)	78 (75 to 81)	11.5 (10.1 to 12.9)	5.8 (4.9 to 6.7)	\downarrow
ACTs for malaria	None†	0.08 (-0.01 to 0.17)	53 (49 to 56)	_	92.8 (79.9 to 105.7)	
ITNs	2 (2 to 3)	25 (23 to 26)	46 (42 to 49)	42.1 (39.3 to 44.8)	8.7 (7.7 to 9.7)	\downarrow
ORS use	47 (42 to 52)	50 (46 to 53)	61 (57 to 64)	1.0 (0.0 to 2.0)	2.8(2.0 to 3.7)	\uparrow

IPTp – intermittent preventive treatment of malaria for pregnant women, ITNs – percent of children <5 who slept under an Insecticide Treated Net the previous night, DPT – diphtheria, pertussis and tetanus, ACTs – Artemisinin–combination therapies, ORS – Percentage of children <5 with diarrhoea in the last 2 weeks who received oral rehydration salts

*Amongst children aged 12-23 moths.

†ACTs were only introduced as first line malaria treatment in 2008.

Arrows in the last column indicate whether average annual change in coverage decreased, was stable or increased between period 1 and period 2: \downarrow - decrease in AAC between pre–CI (period 1) and during CI (period 2); \rightarrow – stable AAC between pre–CI (period 1) and during CI (period 2), \uparrow – increase in AAC between pre–CI (period 1) and during CI (period 2).

Statistical analysis

We used a direct method for estimating under-5 mortality based on the synthetic cohort approach [18,19]. Under this concept, age-specific mortality probabilities for narrow age ranges and defined periods are calculated using death events and exposures. These probabilities are combined to compute the probability that a child has not died before reaching age 5 years [19]. Five-periods were used beginning with five years before the survey, and survival probabilities were calculated over age ranges; 0, 1–2, 3–5, 6–11, 12-23, 24-35, 36-47, 48-59 months as recommended by DHS (Section C in Online Supplementary Document) [19]. The standard errors for the computed mortality estimates were obtained using the Jackknife variance estimation, a repeated sampling method [18]. A series of mortality estimates were obtained by deleting and replacing each primary sampling unit; this produced a sample of under-5 estimates, from which the variance was computed in turn. We also estimated the AAC in mortality using mortality estimates for the periods 1991–1995 and 2006–2010 (Section C in Online Supplementary Document).

For analysis of intervention coverage, the 10 CI districts were treated as one stratum. We re–calculated all relevant coverage indicators from each survey data set in order to obtain the confidence intervals around the estimates. We then assessed whether there was a significant difference in the AAC in coverage for 11 indicators between the pre–CI period (2000–2006) and the CI implementation period (2006–2013) for the 10 CI districts. The 95% confidence intervals (95% CI) around the AAC on the log scale were based on standard deviations calculated using the delta method for the log function of a proportion.

The 95% confidence intervals were used to assess whether the changes were significantly different between pre–CI and CI periods. In order to check the hypothesis that the simultaneous national scale up of iCCM would result in similar coverage change between CI and non–CI districts (supported by other partners), we calculated AAC in intervention coverage in CI and non–CI districts between 2000 and 2010 (data for the non–CI districts was not collected in the 2013 LQAS).

To assess the contribution of iCCM by HSAs, data relating to care and treatment sought for fever, suspected pneumonia and diarrhoea by place of treatment were extracted from the available household surveys. The 2006 MICS only collected data on place of treatment for suspected pneumonia but not for diarrhoea or fever [20] and it was therefore not included in this analysis.

The sampling design of the household surveys such as regional and rural/urban stratification, clustering at enumeration areas and sampling weights (due to non–proportional sampling) were taken into account. We used Stata (version 12) for these analyses [21].

An attempt to quantify the association between change in contextual factors and intervention coverage with change in under–5 mortality in a multivariate analysis did not yield

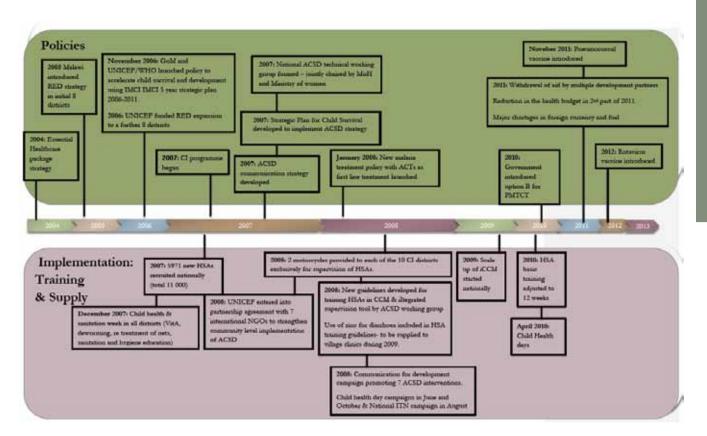


Figure 2. Major policy changes and programmatic activities related to child survival in Malawi (Catalytic Initiative districts and nationally), 2004 – 2012. RED – Reach Every District Strategy; ACSD – Accelerated Child Survival and Development policy; GoM – Government of Malawi; IMCI – Integrated Management of Childhood Illness; MoH – Ministry of Health; CI – Catalytic Initiative; ACTs – Artemisinin–combination therapies for the treatment of malaria; HSA – Health surveillance assistant; NGO – Non-governmental organisation; ITN – insecticide-treated bed net.

meaningful results due to the limited number of data points for macroeconomic contextual variables (Section D in **Online Supplementary Document**).

We used the Lives Saved Tool (LiST) [22] to forecast child mortality (rates and deaths) in the 10 CI districts in 2013 on the basis of the above measured baseline values of mortality in children younger than 5 years for the period 2006-2010 (Section E in **Online Supplementary Document**) and interpolated changes in coverage from the MICS 2006, DHS 2010 and LQAS 2013. We present the estimates of lives saved in 2013, relative to 2008 when CI implementation began, and used the LiST model to investigate the extent to which the declines in child mortality could be attributed to changes in intervention coverage. We also considered the proportion of deaths averted between 2000 and 2008 using our measured baseline mortality and coverage data from the DHS 2000, MICS 2006 and DHS 2010 to compare results between pre-CI and CI periods. The LiST modelling methods have been widely published, including discussion of the limitations which are particularly related to the lack of population-based coverage data for certain key interventions [22-24].

Specific input values used in this LiST application are available in Table s6 in **Online Supplementary Document**. The analysis was done with the computer programme Spectrum/ Lives Saved Tool, version 5.04. The study received ethical approval from the ethics committee of the South African Medical Research Council (EC021–9/2012).

RESULTS

The mortality rate in children younger than 5 years decreased rapidly in the 10 CI districts from 219 child deaths per 1000 live births (95% CI 189–249) in the period 1991–1995 to 119 child deaths per 1000 live births in the period 2006–2010 (105–132) with an average annual change of –4.1%. The mortality decline was similar nationally and in the non–CI districts (**Figure 3**).

Improvements in the coverage of interventions relevant to child survival in the 10 CI districts across the time period 2000 to 2013 were found with regard to all indicators except vitamin A supplementation (**Table 1**). For certain indicators the AAC was higher in the CI period compared to the pre–CI period (early breastfeeding (initiation within 1

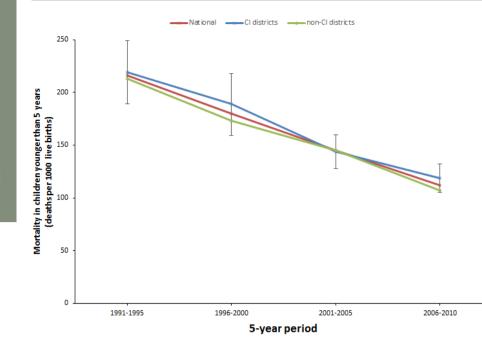
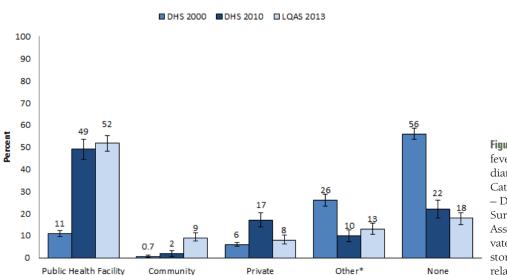


Figure 3. Under–5 mortality rates from 1991 to 2010 in Malawi. Data are from analysis of the 2010 national DHS survey in Malawi. Vertical lines show 95% CIs for survival probabilities for the Catalytic Initiative district estimates. Dates on the x–axis represent the 5–year periods preceding the 2010 Malawi DHS.

hour), measles immunisation and oral rehydration salts (ORS) use) whilst for others (DPT3 immunisation and intermittent preventive treatment of malaria for pregnant women (IPTp) the coverage increases were maintained at the same rate as the pre–CI period. The AAC decreased during the CI period for tetanus toxoid vaccination for pregnant women, exclusive breastfeeding, vitamin A supplementation, care–seeking for pneumonia and insecticide–treated bednets (ITNs) (**Table 1**). While AAC with regard to care seeking for pneumonia and ITNs was not as large during the CI period, both the pre–CI and CI periods reflected gains in coverage.

The AAC in coverage for the examined high impact child health interventions in the CI districts compared to the non CI districts between 2000 and 2010 showed no statistically significant difference for any of the indicators (Table s7 in **Online Supplementary Document**), meaning that although coverage levels differed by intervention and by district, the AAC was consistent across the country for each intervention examined.

The effect of the introduction of HSA delivered iCCM can be seen in the 'place of treatment' data. **Figure 4** shows a steady and significant increase in care–seeking for fever, suspected pneumonia and diarrhoea at community level (HSAs at village clinics) from less than 1% in 2000 to 9% in 2013 with a corresponding significant decrease in children receiving no care from 56% in 2000 to 18% in 2013.



Given the mortality declines and increases in coverage of critical interventions for child survival, the lives saved analysis predicted an under–5 mortality rate in the 10 CI dis-

> **Figure 4.** Place of treatment for fever, suspected pneumonia and diarrhoea in children under–5, 10 Catalytic Initiative districts. DHS – Demographic and Health Survey, LQAS – Lot Quality Assurance Survey. *Other – Private pharmacy, drug vendor/ store, shop, traditional healer, relative/friend.

tricts of 84 per 1000 live births in 2013 when starting at a baseline mortality rate of 119 per 1000 live births in 2008.

The proportion of child lives saved in 2013, by intervention, was calculated using the LiST estimation of 10800 additional deaths averted in 2013 (relative to the 2008 baseline) as a denominator (Figure 5). The pneumococcal vaccine introduction in 2011, with rapid scale up given the existing immunisation platform was estimated to have averted one in four deaths and was the single largest contributor to lives saved in 2013 (24%, 2600 lives saved), followed by ITNs for households (19%, 2100 lives saved) and malaria treatment with artemisinin-combination therapies (15%, 1700 lives saved). Care seeking for suspected pneumonia contributed to 7% of lives saved in 2013 (800 lives saved for pneumonia) and case management of diarrhoea (ORS and zinc) contributed to 5% (400 lives saved for oral rehydration salts (ORS) and 150 for zinc for treatment of diarrhoea). Changes in breastfeeding practices contributed to approximately 6% of deaths averted (600 lives saved). Facility deliveries in the CI districts increased 29 percentage points (from 55% to 84%) in the CI period resulting in improvements in care at birth. These interventions accounted for 11% of all deaths averted even though this was not a direct focus of the CI programme. Of the remaining interventions, no single intervention saved more than 3% of child lives in 2013 (**Figure 5**). Stunting and wasting rates did not decline resulting in no measurable mortality reduction from interventions to address stunting and wasting. When comparing the pre–CI and CI periods, the proportion of deaths averted pre–CI was 15% in 2007 compared to baseline mortality in 2000, whereas during the CI period, the proportion was nearly double at 30% in 2013 compared to 2008 baseline mortality.

Major policies and programmes related to child survival were initiated in Malawi between 2004 and 2011 (**Figure 2**). The Essential Health Package in 2004 prioritised and strengthened community participation and delivery of free community health services through a set of evidence–based high impact interventions for children and adults. In 2005 the Reach Every District strategy was adopted to increase access to these interventions. In 2006, the Government of Malawi, together with UNICEF, WHO and the World Bank launched the Accelerated Child Survival and Development (ACSD) strategy which is an integrated approach based on the IMCI 5–year strategic plan 2006–2011 [25]. Implementation of the CI programme began in 2007 in support

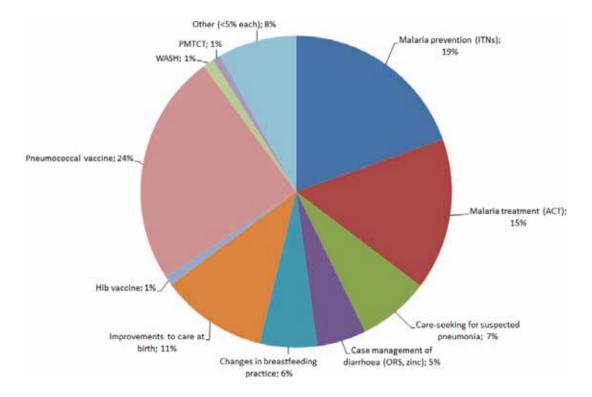


Figure 5. Percentage of child lives saved in Malawi (10 Catalytic Initiative districts), by intervention, in 2013, relative to a 2008 baseline. Improvements to care at birth include: labour and delivery management, antenatal corticosteroids for preterm labour, neonatal resuscitation, and clean birth practices. WASH indicators include improved water and sanitation and access to water connection in the home. ITNs – Percent of children <5 who slept under an Insecticide Treated Net the previous night; ACT – Artemisinin–combination therapy; ORS – Percentage of children <5 with diarrhoea in the last 2 weeks who received oral rehydration salts; PMTCT – Prevention of mother to child transmission of HIV; WASH – water, sanitation and hygiene; Hib – *Haemophilus influenzae* type B vaccine.

of the ACSD policy [8]. In 2008 guidelines for implementation of iCCM were developed and training of existing HSAs began across the country.

The desk review identified improvements in several macroeconomic indicators (**Table 2**). Between 2000 and 2012 there were noticeable changes in the per capita GDP which increased by \$ 110 per capita (in constant 2011 international dollars), from \$ 639 in 2000 to \$ 749 in 2012 [2]. Per capita total expenditure on health increased from \$ 9 in 2000 to \$ 24 in 2012. Although external funding for health had been declining since 2006, it remained substantial at 53% of total expenditure for health in 2012, and more than double what it was in 2000 (26%). The poverty headcount (<\$ 1.90/ day) declined from 74% in 2004 to 71% in 2010 [2].

A major set–back occurred in 2011 due to a successive combination of the impact of the global economic crisis and the withdrawal of funding locally by bilateral and multilateral partners from the Sector Wide Approach (SWAp) [26]. These events led to the devaluation of the Malawi currency as well as severe shortages in foreign currency and fuel. With Malawi's extreme dependence on foreign aid, the country's health budget was substantially reduced in the second quarter of 2011. Development assistance to the SWAp has not resumed but direct funding of projects by partners continues.

DISCUSSION

Our results show that Malawi, one of the least developed countries in the world, ranking 170 out of 187 on the Human Development Index in 2012 [27], has managed to reduce under–5 mortality in the 10 CI districts by 100 deaths

per 1000 live births (a 46% reduction) between 1991 and 2010. This has occurred in the context of changes, mainly at the policy and budgetary level, including increases in funding from both the government and donors [28], which enabled a conducive environment for implementation of the nation's ambitious child survival policies.

The coverage of many priority child health interventions increased significantly since 2000, particularly preventive interventions including IPTp, immunisations and use of ITNs, as well as health behaviours such as early and exclusive breastfeeding and care–seeking for suspected pneumonia. The health interventions that account for the majority of the deaths averted are delivered at village clinic level through both outreach and stimulating increased demand (eg, immunisation, ITN distribution, care–seeking behaviours and treatment coverage). A number of high impact interventions increased in coverage at a higher rate than prior to the CI implementation. A similar AAC in coverage between 2000 and 2010 was seen in all districts across the country, evidence of the Ministry's approach of scaling up high impact interventions across the entire country.

The contextual analysis provides insight into the lack of difference in mortality and coverage change between the CI and non–CI districts. The implementation of the Strategic Plan for Child Survival and subsequent scale up of iCCM occurred simultaneously across the whole country supported by a collective of partners and donors allocated to each of the 28 districts with a partnership agreement to guide implementation. Although the 10 CI districts were the focus of DFATD support, other donors implemented the same packages of support in the remaining 18 districts.

Our findings suggest that several factors worked synergistically to achieve the decreases in child mortality in Malawi.

Table 2. Comparison of broader health system and non-health system changes between 2000 and 2012 that might be expected to affect child survival

		Year			
Indicator	2000	2006	2010	2012	
Gross domestic product per capita (PPP, constant 2011 international \$)*	639	612	749	749	
Total fertility rate	6.2	5.8	5.6	5.4	
Female completion of lower secondary school	16% (1999)	13%	12%	12%	
Per capita total expenditure on health	\$9	\$21	\$30	\$24	
Total government expenditure on health (% of GDP)	6%	9%	8%	9%	
External resources for health (% of total expenditure)	26%	59%	55%	53%	
HIV prevalence (15–49 years)	15.8%	12.9%	11.2%	10.8%	
Poverty headcount ratio @<\$1.90 a day (2011 PPP)†	64% (1997)	74% (2004)	71%		

*GDP per capita based on purchasing power parity is gross domestic product converted to international dollars using purchasing power parity rates. An international dollar has the same purchasing power over GDP as the US dollar has in the United States. Data are in constant 2011 international dollars. Source: World Bank database [2].

*Poverty headcount ratio at \$1.90 a day is the percentage of the population living on less than \$1.90 a day at 2011 international prices.

First, these improvements have taken place within a context of strong child health policies and clear leadership of the Ministry of Health, which, although donor dependent, channelled support in a co-ordinated manner to effectively implement national child survival policies [10,29,30]. This finding reinforces previous results from analyses of success factors related to declines in neonatal mortality in Malawi [13,31]. Second, the implementation of these policies and high impact interventions has been made possible through substantial external investments in the health system, particularly the contribution of donors. The official development assistance to maternal, child and newborn health in Malawi increased from US\$ 51.7 million in 2003 to US\$154.7 million in 2012 [28]. Third, investments in the capacity of the health work force has plausibly led to improvements in important health behaviours such as use of ITNs, facility deliveries, immunisation coverage, careseeking and treatment for common childhood illnesses. These investments include strengthening, over decades, a dense network of over 10000 HSAs nationally as well as the Emergency Human Resource Programme launched in 2004 leading to a doubling of professional health workers (including doctors, clinical officers and nurses) [32].

While HSAs play a very important role in the health system, the contribution that community level care (through HSAs) has made to child survival should not be overstated. While the 7 percentage point increase in care-seeking at the community level is substantial in a context where careseeking at this level was 2% at the start of iCCM scale-up and almost non-existent prior to this, it does point to a need for greater efforts to generate demand for community care-seeking. However, it should be noted that there is a theoretical ceiling for treatment of childhood illness at community level since HSAs delivering iCCM services are situated in hard-to-reach areas and therefore not all communities sampled in household surveys will have been exposed to iCCM-trained HSAs. With just over a third of HSAs trained in iCCM, the Government of Malawi and its partners have yet to fully leverage the potential of this service delivery platform. However, this task-shifting needs to be aligned with investments to enable effective supervision and mentorship of this front-line cadre [33,34].

A strength of this evaluation is that the 10 CI districts are geographically–dispersed across all three regions of the country, thus limiting regional biases. Population–based household survey data on mortality and coverage from all 10 CI districts were available for analysis from the time of implementation of the CI (2006), during the CI period (sampling in 2010), and at the end of the programme (2013). These data were triangulated with an in–country document review to gain a more in depth understanding of the reasons for the quantitative changes in coverage and mortality.

There were weaknesses to this evaluation. First, the lack of oversampling to provide district level coverage estimates for all districts in the 2000 DHS. Although the data were aggregated across the two strata (CI and non-CI districts), there could be regional biases from the pre-CI estimates. A sensitivity analysis revealed no significant changes to the AAC comparisons (Table s8 in Online Supplementary **Document**). Second, due to the mix of methods used to collect contextual data, we are unable to quantitatively estimate the relative contributions of wider changes in the health system and beyond to the reduction of child mortality. However we have followed the approach used in two previous country case studies [35,36], one of which is part of the Countdown to 2015 multi-institutional, multiagency collaboration to track progress towards MDG goals 4 and 5 [36]. This case study will therefore add to the body of literature describing unique national pathways towards improved child survival.

Third, while the LiST model predicted within a margin of the measured mortality change, all factors must be applied when directly linking measured mortality reduction with coverage change. For this reason the results of the LiST analysis should be treated with caution. For example, factors outside of the health sector could have contributed to mortality declines, and/or incorrect assumptions could have been used for coverage of high impact interventions without empirical data available (eg, Kangaroo Mother Care) to run the LiST model.

Malawi has achieved remarkable progress in reducing child mortality and a recently released household survey reports a further decline which will almost certainly enable the country to achieve MDG4 [37]. However, one also needs to consider whether this trend is sustainable given Malawi's heavy reliance on donor funding for the health sector and the risk of shifting global priorities. Malawi provides a strong example for countries in sub-Saharan Africa of how high impact child health interventions implemented within a decentralised health system with an established community-based delivery platform, can lead to significant reductions in child mortality. This example also highlights the imperative for the international community to commit to longer-term investments in health system strengthening and development as countries move from the "quick wins" related to survival to the more complex goals related to overall child health and development.

Ethical approval: This study was approved by the ethics committee of the South African Medical Research Council (EC026–9/2012). Approval was also provided by the UNICEF Malawi country office.

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Authorship declaration: TD and WZ conceptualised the study with inputs from DS, KD, DJ and NO. WZ, TD and KD developed the protocol, study design, and data collection materials. TD, DS, DJ, KD and DB participated in the country evaluation visit in August 2013. SM and NN conceptualised the mortality analysis and data quality assessments, which were done by them. NN led the work on quality assessment and reanalysis of datasets on intervention coverage, with participation by SR, DB, SM, MM and NO. WZ and TD prepared the data and analysis of contextual factors. MK and KK did the LiST analysis. TD, WZ, DS, WvD, DJ, KD, NN, DB, SR, MK, KK and ED participated in a two–day workshop in Cape Town in February 2014, to review and interpret the preliminary results. WZ and TD prepared the first draft of the paper. All authors reviewed and contributed to subsequent drafts and approved the final version for publication.

Competing interests: IR is the editor of the *Journal of Global Health*. To ensure that any possible conflict of interest relevant to the journal has been addressed, this article was reviewed according to best practice guidelines of international editorial organizations. All authors have completed the Unified Competing Interest form at www. icmje.org/coi_disclosure.pdf (available on request from the corresponding author). NO, TZ, MM and DJ are employed by UNICEF; however, only TZ was involved in implementation of the Catalytic Initiative in Malawi. NO, MM and DJ were only involved in the evaluation component. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the views of UNICEF.

Data sharing: No additional data available. DHS and MICS survey datasets are available on request from DHS and UNICEF.

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Global analysis of overweight prevalence by level of human development

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Carmen Ng University of Pennsylvania Graduate Group in Demography 216 McNeil Building 3718 Locust Walk Philadelphia, PA 19104 United States of America ngcarmen@sas.upenn.edu **Background** Less developed countries are increasingly afflicted with over–nutrition, and the escalating overweight prevalence has become a global problem. However, a problem as global as this may not be amenable to a general set of remedial interventions applicable to all countries.

Methods I use data from various sources, including the World Health Organization and the World Bank, to test the association of overweight prevalence with economic, social, and demographic indicators. I then split the countries up by human development index to investigate to what extent these associations vary between development levels.

Findings On a global scale, overweight prevalence is most associated with gross domestic product (GDP) per capita, the proportion of a country that is rural, the proportion of elderly in a country's population, and the average years of schooling. At what magnitude, and even in which direction, these relationships go vary with a country's level of development. Generally, GDP per capita has a positive association with overweight prevalence, with the magnitude of such association for countries of very high human development more than twice of that for countries of low human development. However, proportion rural has a negative association for countries of low human development prevalence, with the magnitude of such association for countries of low human development. All four of these variables have statistically significant association with overweight prevalence in countries with low human development.

Conclusions I make policy suggestions to combat increasing overweight prevalence, based on the models that are developed, paying special attention to the differences in magnitude and direction of the regressors between human development levels.

According to World Health Organization (WHO) statistics, more than a billion adults are overweight. WHO defines adult overweight as having a body mass index (BMI) of 25 kg/m² or above. The rise of overweight prevalence has been an issue in developed countries for years, but it has gained increasing attention in developing countries as an issue that needs to be addressed. Traditionally, being underweight has been a "poor coun-

try's problem," whereas being overweight has been a "rich country's problem." Now, developing countries are plagued with both [1].

The rapid increase in economic development, urbanization, and industrialization has been a major reason for the rise in overweight prevalence in developing countries. This transformation has led to substantial changes in diet and physical activity, an increasing prevalence of being overweight, and accompanying conditions and diseases. Studying overweight prevalence is important because it is a risk factor for many non–communicable diseases, including cardiovascular disease, diabetes, and certain types of cancer [2].

Much research has been conducted on overweight prevalence and accompanying policy recommendations [3,4]. However, a problem as global as this may not be amenable to a general set of remedial interventions applicable to all countries. The difference between developed and developing countries in terms of economic, social, and demographic indicators is so tremendous that the same policies could not be expected to work for both. The purpose of this paper is to analyze adult overweight prevalence in countries at varying degrees of development, measured by such aggregate indicators. I expect the associations of these factors with overweight prevalence to vary between countries at different levels of development, so a one-size-fits-all policy would not work for all countries. I seek to interpret these results, and suggest actions that countries could take, depending on their development level.

METHODS

In this study, a macro approach of investigation is taken, using country–level data from 2002, 2005, and 2010. I choose the above years based on the availability of data from the WHO Global Infobase, a database with information on chronic diseases and their risk factors [5]. The dependent variable is the percentage of overweight adults aged 15 to 100 in a country.

A multitude of variables potentially related to overweight prevalence are considered. Data for these variables are mainly from the World Bank [6]. A data set with information on the number of McDonald's restaurants in various countries, compiled by the Datablog of *The Guardian* newspaper, is also used [7]. Variables in my analysis include the following: gross domestic product (GDP) per capita in 2010 US\$ and adjusted by purchasing power parity, unemployment rate, percentage of population rural, percentage of population aged 65+, average years of total schooling (ages 15+), internet users (per 100 people), and coverage of McDonald's restaurants. The variables GDP per capita, proportion of people aged 65+, and internet users exhibit a non-linear concave pattern when plotted with overweight prevalence, so a natural logarithmic transformation (with an offset) is used to linearize the data.

I use the variable internet users as a proxy for sedentary lifestyles and access to Western culture, and the variable coverage of McDonald's restaurants as a proxy for access to fast food. Coverage is defined as the area of a country (in km²) divided by the number of McDonald's restaurants in the country. For countries that had no McDonald's restaurants, I give them a value of 350 000, which is greater than any of the values for countries with at least one McDonald's restaurant. It is reasonable to assume that if a McDonald's restaurant was not within 350 000 km², a person would not elect to go there. Data for the number of McDonald's restaurants are available for the years 2007 and 2012 (used for my 2005 and 2010 analyses respectively).

To start, I run multiple linear regression models to investigate the association of overweight prevalence with my explanatory variables among all countries. All analyses are run using the statistical package R (version 3.1.1) [8] and a significance level of five percent is used. With overweight prevalence data for multiple years, I further investigate using a panel model. In addition, I would like to take into account the heterogeneity among countries. The Hausman specification test suggests a fixed effects model. For this model, both sexes and the significant variables from the previous models are included.

The Human Development Index (HDI) is a loose indicator of a country's level of development complied by the United Nations Development Program (UNDP). The indicator is determined using three factors—life expectancy, an aggregate measure based on the mean years of schooling for adults and the expected years of schooling for children, and gross national income per capita. The HDI is calculated for most countries, and each country is put into one of four categories – very high (1), high (2), medium (3), or low (4) human development [9]. It should be noted that there are potential issues here with reverse causality. For the rest of the paper, HDI level is used only as a means to separate countries into delineated groups.

One-way analysis of variance (ANOVA) and pairwise testing are used to compare mean overweight prevalence between HDI levels. To ascertain the differences in more detail, I construct fixed effects models for the four HDI levels, and compare the difference in association of overweight prevalence with my explanatory variables between pairs of HDI levels.

RESULTS

There are 192 countries with data on overweight prevalence in 2002, 2005, and 2010. Of these countries, 47 are in the very high, 52 are in the high, 41 are in the medium, APERS

Multiple regression models by sex and year

I run a multiple regression model for each sex and year combination, and the results are presented in **Table 1** and **Table 2**.

For both sexes and all years, log(GDP per capita) and average years of schooling are consistently positively associated with overweight prevalence, whereas proportion rural is consistently negatively associated with overweight prevalence. Associations do not seem to be the same for the two sexes. For example, female overweight prevalence is positively and significantly associated with unemployment, but there appears to be no significant association for males—not even when overweight prevalence is regressed only on unemployment in simple regressions; thus, the multiple regression models for males do not include unemployment.

From the results in **Tables 1 and 2**, the explanatory variables log(internet users) and McDonald's coverage seem to have little association with overweight prevalence. Sedentary lifestyles and unbalanced diets have often been blamed as major players in the "obesity epidemic" in developed countries [10]. However it seems that neither internet use nor proximity to a McDonald's restaurant has a significant association with overweight prevalence when both developed and developing countries are considered in this study.

Aside from the intercept which consistently increases and the coefficient of log(GDP per capita) which consistently decreases over the years, the coefficients of the other variables do not reveal a clear pattern. For the most part, coefficients that were significant in 2002 remained that way in the following years.

Fixed effects model

I include both males and females with the variables from the previous models, except log(internet users) and Mc-Donald's coverage due to their general lack of significance. The results are presented in **Table 3** (additional models are created to include one or both of the variables log(internet users) and McDonald's coverage, but these variables are again found to be generally insignificant).

It seems that countries with higher GDP per capita, populations comprised of more elderly people, and more highly–urbanized areas tend to have higher overweight prevalence. Average years of schooling and unemployment are not significant in this model.

Log(proportion 65+) has switched in sign from my models for females in **Table 2**. A possible reason is that the flexibility of a fixed effects coefficient for each sex and country

 Table 1. Association between male overweight prevalence and economic, social, and demographic regressors using a multiple linear regression model in each year[†]

	2010	2005	2002
Intercept	-11.3 (19.4)	-24.1 (19.2)	-28.3 (18.7)
Log(GDP per capita)	4.71 (2.29)*	6.50 (2.15)**	6.87 (2.11)**
Proportion rural	-0.189 (0.083)*	-0.148 (0.0832)	-0.188 (0.0792)*
Log(proportion 65+)	-0.145 (2.34)	1.46 (2.67)	2.20 (2.70)
Average years of schooling	1.63 (0.741)	1.61 (0.709)*	1.78 (0.718)*
Log(internet users per 100 people)	2.32 (2.51)	-0.150 (2.20)	-1.65 (1.99)
McDonald's coverage	$-9.82 \times 10^{-7} (1.02 \times 10^{-5})$	$-6.22 \times 10^{-6} (1.05 \times 10^{-5})$	N/A

N/A – not applicable

*Coefficient estimates are displayed with standard errors in parentheses. ** – significance at 1%, * – significance at 5%.

Table 2. Association between female overweight prevalence and economic, social, and demographic regressors using a multiple linear
regression model in each year†

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	2010	2005	2002
Intercept	31.7 (21.0)	25.4 (20.3)	13.7 (20.1)
Log(GDP per capita)	2.02 (2.47)	2.43 (2.27)	4.03 (2.25)
Unemployment	0.542 (0.236)*	0.724 (0.205)***	0.649 (0.196)**
Proportion rural	-0.236 (0.090)*	-0.169 (0.0884)	-0.193 (0.0855)*
Log(proportion 65+)	-7.84 (2.54)**	-9.13 (2.83)**	-7.70 (2.87)**
Average years of schooling	0.998 (0.804)	0.909 (0.756)	1.01 (0.786)
Log(internet users per 100 people)	3.42 (2.71)	4.37 (2.34)	1.80 (2.19)
McDonald's coverage	7.78×10 ⁻⁷ (1.13×10 ⁻⁵)	$-4.46 \times 10^{-6} (1.12 \times 10^{-5})$	N/A

N/A – not applicable

*Coefficient estimates are displayed with standard errors in parentheses. *** – significance at 0.1%, ** – significance at 1%, * – significance at 5%.

Table 3. Association between overweight prevalence and
economic, social, and demographic regressors in a fixed effects
model (both sexes, all years)†

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Log(GDP per capita)	5.74 (0.533)***
Unemployment	0.00457 (0.0426)
Proportion Rural	-0.454 (0.0528)***
Log(Proportion 65+)	2.49 (1.08)*
Average years of schooling	-0.183 (0.145)

*Coefficient estimates are displayed with standard errors in parentheses. *** – significance at 0.1%, * – significance at 5%.

combination allows the coefficients of the regressors more "freedom" to reflect their actual effects. If so, the independent variable log(proportion 65+) seems to have a positive association with overweight prevalence. Previous research on seven middle– and low–income countries has found that overweight prevalence is typically higher for older females, and it would make sense for this result to generalize to countries with older populations [11].

Figure 1 shows boxplots of the fixed effects for each sex and HDI level. If all countries and sexes were homogeneous, in terms of overweight prevalence, I would expect their fixed effects to be about the same. However, that does not appear to be the case. It is interesting that the fixed effects for the females—low human development combination are relatively high even though females in these countries typically have lower overweight prevalence. If the model remains valid, females in countries in the low human development category would be especially at risk of seeing very high overweight prevalence levels as development continues in these countries.

Analysis by level of development

It appears in **Figure 2** that overweight prevalence varies among different levels of development. For each sex and year combination, one–way ANOVA rejects the null hypothesis that the means of overweight prevalence are the same among all four HDI levels. To see which levels have

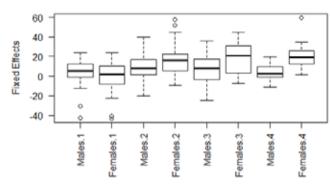


Figure 1. Fixed effects from overweight prevalence fixed effects model. The horizontal axis labels are in the form: sex, Human Development Index (HDI) level (1 for very high, 2 for high, 3 for medium, 4 for low).

statistically different values of mean overweight prevalence, I perform pairwise t-tests with the Holm–Bonferroni adjustment to correct for multiple testing. For males in all years, the mean overweight prevalence at each HDI level is statistically different from that at every other level. For females in all years, the means of overweight prevalence are statistically different in all pairwise comparisons, other than between very high and high, and between very high and medium. Thus, overweight prevalence in countries seems to vary by their level of development. To delve into this further, I run a fixed effects model for each HDI level. The results of the model are displayed in **Table 4**.

For every pair of HDI levels, I compare the coefficients of each independent variable. To this end, a regression model is created for each pair of HDI levels with added variables for HDI level and interactions of all of my predictors with HDI level. The results of this are shown in **Table 5**. Note that the interaction estimates are consistent with the results in **Table 4**.

The coefficients of unemployment are not significantly different between any pair of HDI levels, nor is this regressor

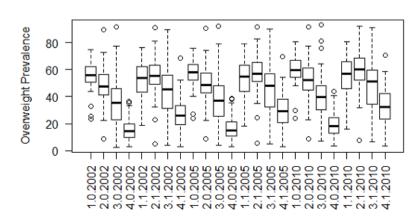


Figure 2. Boxplots of overweight prevalence by HDI level, sex, and year. The horizontal axis labels are in the form: Human Development Index (HDI) level (1 for very high, 2 for high, 3 for medium, 4 for low), indicator for sex (1 for female, 0 for male), and year.

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	Very high	Нідн	Медіим	Low
Log(GDP per capita)	7.78 (0.883)***	2.84 (1.10)*	8.75 (1.28)***	3.09 (1.19)
Unemployment	0.0405 (0.0594)	-0.0861 (0.0891)	0.00154 (0.125)	-0.160 (0.121)
Proportion rural	-0.423 (0.114)***	-0.203 (0.122)	-0.186 (0.121)	-0.757 (0.0940)***
Log(Proportion 65+)	-0.295 (1.24)	16.1 (4.17)***	4.84 (2.79)	10.9 (3.66) *
Average years of schooling	-0.0467 (0.211)	0.132 (0.340)	0.205 (0.305)	-1.00 (0.311)**

 \dagger Coefficient estimates are displayed with the standard errors in parentheses. *** - significance at 0.1%, ** - significance at 1%, * - significance at 5%.

Table 5. Interactions between economic, social, and demographic regressors and Human Development Index levels from pairwise	;
tests	

	Very high vs high	Very high vs medium	VERY HIGH VS LOW	High vs medium	HIGH VS LOW	Medium vs low
Log(GDP per capita)	-4.94 (1.39)***	0.975 (1.53)	-4.69 (1.50)**	5.92 (1.76)***	0.248 (1.75)	-5.67 (1.75)**
Unemployment	-0.127 (0.103)	-0.0389 (0.135)	-0.201 (0.138)	0.0877 (0.163)	-0.0741 (0.168)	-0.162 (0.175)
Proportion rural	0.220 (0.168)	0.236 (0.165)	-0.334 (0.148)*	0.0166 (0.177)	-0.554 (0.158)***	-0.570 (0.152)***
Log(Proportion 65+)	16.4 (3.88)***	5.14 (2.97)	11.2 (3.97)**	-11.3 (4.95)*	-5.23 (5.80)	6.06 (4.71)
Average years of schooling	0.179 (0.382)	0.252 (0.365)	-0.953* (0.382)	0.0725 (0.465)	-1.13 (0.485)*	-1.20 (0.440)**

*Coefficient estimates are displayed with the standard errors in parentheses. *** – significance at 0.1%, ** – significance at 1%, * – significance at 5%.

even significant for any HDI level in the fixed effects models. Each pair of HDI levels has at least a couple of variables with significantly different coefficients, with one notable exception. Very high human development and medium human development do not have significantly different coefficients for any variable. It is interesting to note that the means of overweight prevalence are not significantly different between these two levels for females in any year as well. For the most part, the coefficients in the models for the top three HDI levels are pretty different from those for the low human development level.

DISCUSSION

From the multiple regression models by sex and year, it seems that the associations of overweight prevalence with the economic indicators log(GDP per capita) and unemployment are different for the two sexes, and seem to point in opposite directions. Log(GDP per capita) is consistently positive and significant for males but not for females, while unemployment is consistently positive and significant for females but not for males. This would seem to indicate that males and females tend to be more overweight when the economy is doing well and poorly, respectively. Countries at all levels of development might benefit by offering women with guidance and counseling during economic downturns, and by providing men with reminders to watch their diets and not to forego exercise even while working in a booming economy.

The variable proportion rural is negatively and significantly associated with overweight prevalence in most of my models. In addition, its partial slope in the model for low human development countries is more negative and significantly different from those for other development levels. Previous research among women aged 20 to 49 in a collection of developing countries found that overweight prevalence is about twice as high in urban areas than in rural ones [12]. The negative and significant coefficient of this variable for the very high human development countries is harder to decipher, as research results on urban-rural disparities in these countries have been conflicting [13-15]. Perhaps countries at the very high human development level, ranging from the United States to France to Saudi Arabia, are too heterogeneous. The coefficient of the proportion rural variable is consistently negative, and urbanization decreases such proportion. Countries, especially those with low human development, should make maintaining a generally healthy living environment and establishing quality health care services a priority, as development and urbanization typically occur concurrently.

Log(proportion 65+) is positive and significant in the overall fixed effects model and two of the fixed effects models by HDI. Overweight prevalence appears to be a risk factor for the elderly, and more so for females than males. More assistance for and supervision of elderly females could help reduce overweight prevalence.

Among the four development levels, average years of schooling is significant and negatively associated with overweight prevalence at the low human development level, and this partial slope is significantly different from those in the models for other development levels. For countries at the bottom level of development, education is of the utmost importance. Health education in the least developed countries could help by leaps and bounds in preventing not just overweight prevalence, but also other health conditions. Preventative measures directed toward school children could do more than curative care targeted at already overweight individuals. In addition, more educated parents would likely provide better prenatal and postnatal care, thereby reducing the risk of their children being overweight.

In the individual sex and year models, the coefficient on average years of schooling is always positive and significant for males. How can this sign switch be explained? People with more education are typically wealthier, busier, and have more access to and options for food – all risk factors for increased BMI. In poorer countries though, an additional unit of schooling could substantially contribute to a person's knowledge of health and/or ability to eat a balanced meal. In a study of reproductive–age women in Egypt, education was found to counter the effects of increasing wealth on overweight prevalence [16].

There are some caveats that should be kept in mind. UNDP switched its method of categorization in 2014 from one based on quartiles to one based on fixed cut-off points. With quartile groupings, a country moving up a quartile necessarily meant that another country would have to move down, even if that country's level of development had actually improved. However, the fixed cut-offs that have recently been adopted by UNDP might not necessarily work for data from more than a decade ago. Despite their shortcomings, the groupings provided by UNDP in 2013 are used in this study. Countries could have moved between levels and a country's categorization in 2013 might not be the same as its categorization in 2002, 2005, or 2010, but the UNDP finding that few countries even changed ranks (let alone human development levels) between 2012 and 2013 makes this concern less worrisome [17].

Some of these variables are relatively highly correlated, especially with log(GDP per capita). However, most of the coefficients make sense and are interpretable. Additionally, I check the variance inflation factors to ascertain the severity of this problem for all my regression coefficients in each individual sex and year multiple regression model. All variables have factors well below the criterion indicating a concern.

A few additional comments on the variables are in order. Internet users and McDonald's coverage are only proxies. They are not stand—ins or perfect numerical representations of sedentary lifestyles and access to Western culture or access to fast food. Additionally, any factors that might be related to overweight prevalence necessarily have a lagging effect. I have not taken such a lag into consideration. Perhaps a one—year lag or a combination of prior values could be used instead in further studies.

It is clear that overweight prevalence is a global problem. However, this is *not* a problem that all countries in the world can address in the same way. Generally, GDP per capita, the proportion of a country that is rural, the proportion of elderly in a country's population, and the average years of schooling are significantly associated with overweight prevalence. Yet the association and significance that each of these variables has on overweight prevalence varies greatly by a country's level of human development.

I have made some policy recommendations based on my analysis. However, caution is in order. While it seems from the results that increasing GDP per capita would be connected with an increase in overweight prevalence, my conclusion is definitely not to advise policymakers to slow down the development of their countries. Instead, while policymakers try to improve the well–being of their fellow citizens, they should not unwittingly exacerbate the possible ill effects of development, such as increasing overweight prevalence.

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Authorship declaration: The ideas, analyses, and research in this paper are all the author's own work.

Competing interests: The author has completed the Unified Competing Interest form at www.icmje. org/coi_disclosure.pdf (available on request from the author). The author has no conflicting financial or other interest related to the work detailed in this manuscript.

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Scaling–up public sector childhood diarrhea management program: Lessons from Indian states of Gujarat, Uttar Pradesh and Bihar

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Sanjeev Kumar Manager–Monitoring and Evaluation Micronutrient Initiative, India B 28, Qutab Institutional Area Tara Crescent New Delhi 110016 sakumar@micronutrient.org **Background** Diarrhea remains a leading cause of death among children under five in India. Public health sector is an important source for diarrhea treatment with oral rehydration salts (ORS) and zinc. In 2010, Micronutrient Initiative started a project to improve service delivery for childhood diarrhea management through public health sector in Gujarat, Uttar Pradesh (UP) and Bihar. This paper aims to highlight feasible strategies, experiences and lessons learned from scaling–up zinc and ORS for childhood diarrhea management in the public sector in three Indian states.

Methods The project was implemented in six districts of Gujarat, 12 districts of UP and 15 districts of Bihar, which includes 10.5 million children. Program strategies included capacity building of health care providers, expanding service delivery through community health workers (CHWs), providing supportive supervision to CHWs, ensuring supplies and conducting monitoring and evaluation. The lessons described in this paper are based on program data, government documents and studies that were used to generate evidence and inform program scale–up.

Results 140000 health personnel, including CHWs, were trained in childhood diarrhea management. During three years, CHWs had sustained knowledge and have treated and reported more than three million children aged 2–59 months having diarrhea, of which 84% were treated with both zinc and ORS. The successful strategies were scaled–up.

Conclusion It is feasible and viable to introduce and scale–up zinc and ORS for childhood diarrhea treatment through public sector. Community–based service delivery, timely and adequate supplies, trained staff and pro–active engagement with government were essential for program success.

Diarrhea remains one of the leading causes of death among children under 5 in the world, causing 9.2% of total under 5 child deaths [1]. In India childhood diarrhea contributes to nearly 12.6% of all deaths in children below five years [2], which is nearly 2 million child deaths annually. Despite a decline in diarrheal deaths [1], the high mortality and disease burden due to diarrhea underscores the need for urgent attention. It has been found that zinc when given for the treatment of diarrhea reduces diarrhea mortality by 23%, decreases the severity of the initial episode, and may prevent future diarrheal episodes in the 2–3 months following supplementation [3].

ORS is a simple, proven treatment that can be used to prevent and manage dehydration and decrease in diarrhea mortality. In a meta–anlaysis of ORS intervention studies, 69% pooled relative reduction has been noticed in diarrhea mortality in communities in which ORS was promoted compared with comparison areas. Use of ORS also results in 29–89% relative decreases in referrals to health centres in the intervention areas. [4].

To manage childhood diarrhea and reduce diarrhea–related mortality and morbidity, WHO and UNICEF have recommended the use of both ORS and zinc for diarrhea treatment [5], which has also been adopted by the Government of India. The duration of treatment with zinc for all children in the age group 2–59 months is 14 days and the recommended dosage is 10 mg of zinc per day for children 2–6 months of age and 20 mg per day for children 6–59 months of age, as per these guidelines. Despite this renewed focus, there has been slow progress in operationalizing these guidelines and diarrhea prevalence remains high at 11.7% in India [6]. Zinc is still not being used at scale in combination with ORS under government programs resulting in low coverage of zinc [7].

Micronutrient Initiative (MI) has been a pioneer organization in demonstrating childhood diarrhea management with zinc as an adjuvant to ORS among large populations, and understanding its feasibility for scale–up through the public health sector (including government hospital, primary health center–PHC, sub center, auxiliary nurse midwife–ANM, accredited social health activist–ASHA) and anganwadi workers–AWW). MI has implemented childhood diarrhea management projects in the three Indian states of Gujarat, Uttar Pradesh (UP) and Bihar.

The programs focused on:

- Creating a positive enabling environment, building commitment and sustainability for diarrhea management in the implementation states, and
- Improving availability of supplies at the point–of– care for treating childhood diarrhea

The lessons from these projects along with earlier demonstration projects helped to facilitate the scale–up and mainstreaming of therapeutic zinc supplementation and oral rehydration for treatment of childhood diarrhea through public sector channels. In all three states, the care seeking for childhood diarrhea in private sector is high (**Table 1**). However, scope of this paper is limited to the experiences of implementing childhood diarrhea management program through public sector.

Our study aims to highlight: 1) feasible program strategies which could be used to strengthen and scale–up childhood diarrhea management program, and 2) key lessons learned in scaling–up of zinc and ORS treatment for childhood diarrhea through the public sector.

PROGRAM

The methodology adopted includes use of program monitoring data, findings of research studies, government documents and data from government surveys to provide evidences for key achievement and draw lessons and conclusions. The main sources of data used in the paper include program reporting and monitoring through government system, periodic supply audit studies and other research studies carried out through external research organizations under this program such as rapid assessment of treated child diarrhea cases, caregivers practice and ac-

	Gujarat (%)	Uttar Pradesh (%)	Bihar (%)
Children under five with diarrhea in the last two weeks (DLHS-3, 2007-08) [6]	11.8	16.2	12.1
Care-seeking for diarrhea from any source (DLHS-3, 2007-08) [6]	65.6	73.8	73.6
Care–seeking for diarrhea in public sector (Public sector includes Government hospital or dispensary, urban health centre/ urban health post/ urban family welfare centre, community health centre or rural hospital, primary health centre, sub–centre, ICDS and Government AYUSH hospital/clinic) (DLHS–3, 2007–08) [6]	43.7	10.4	6.1
Care-seeking in private sector (Private sector includes non-governmental hospital/ trust hospital or clinic, private hospital/clinic and private AYUSH hospital /clinic) [6]	56.0	82.7	56.6
Children suffering with diarrhea treated with ORS (DLHS-3, 2007-08) [8]	36.7	17.4	22
Children suffering with diarrhea not receiving any treatment (DLHS-3, 2007-08) [6]	34.4	26.2	26.4
Use of zinc for diarrhea treatment (among the children having diarrhea in last two weeks) (NFHS-3, 2005-06) [7]	0.0	0.5	0.0

DLHS 3 – District Level Household Survey–3 (DLHS-3), ICDS – Integrated Child Development Services, AYUSH – Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy, NFHS 3 – National Family Health Survey 3

*Since program evaluation data are not being used in this paper, data from NFHS 3 (2005–2006) and DLHS 3 (2007–2008) have been used as these are the most recent data available prior to initiation of the projects. For indicator on use of zinc for diarrhea treatment, NFHS 3 data has been used as this indicator is not there in DLHS 3.

ceptability of frontline workers as credible providers and process evaluation of supportive supervision under childhood diarrhea management program.

Key strategies and challenges faced under the program have been described to give better understanding of implementing the program at scale.

Program area and demographic information

The project was implemented in UP and Gujarat between 2010 and 2014 and in Bihar between 2010 and 2015. In Gujarat and Bihar, the projects were initially implemented in 6 and 15 demonstration districts, respectively and subsequently scaled—up across the entire state by the respective state governments. In UP, the program was implemented in 12 districts under the Diarrhea Alleviation through Zinc and ORS Therapy (DAZT) project (**Figure 1**). The states and districts were selected based on high prevalence of childhood diarrhea and feasibility of program implementation. **Table 2** further describes the intervention areas. The largest program was in Bihar with 15 demonstration districts and 23 scale—up districts, which reached an estimated population of 13211546 children aged 2–59 months.

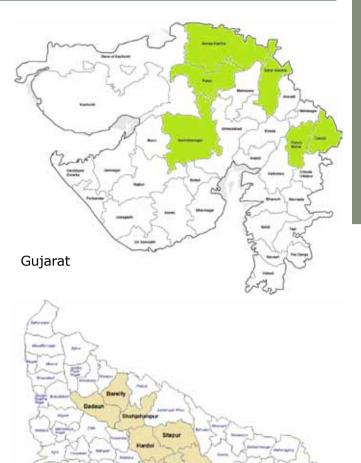
DAZT districts of Gujarat: In Gujarat, the demonstration project was implemented in six out of 26 districts: 1. Sabarkantha, 2. Patan, 3. Banaskantha, 4. Surendranagar, 5. Panchmahal, 6. Dahod.

DAZT districts of Uttar Pradesh: In Uttar Pradesh, the demonstration project was implemented in 12 out of 75 districts: 1. Ambedkar Nagar, 2. Kanpur Dehat, 3. Barabanki, 4. Lucknow, 5. Bareilly, 6. Shahjahanpur, 7. Budaun, 8. Sitapur, 9. Faizabad, 10. Sultanpur, 11. Unnao, 12. Hardoi.

DAZT districts of Bihar: In Bihar the demonstration project was implemented in 15 out of 38 districts: 1. Banka, 2. Bhagalpur, 3. Samastipur, 4. Sitamarhi, 5. Sheohar, 6. Munger, 7. Madhepura, 8. Sharsha, 9. Khagaria, 10. Supaul, 11. Nalanda, 12. Sheikhpura, 13. East Champaran, 14. Gaya, 15. Jehanabad.

Table 1 shows the situation of childhood diarrhea care seeking and treatment prior to the implementation of the DAZT programs across the three states. Care–seeking for diarrhea was at 65.6% in Gujarat, 73.8% in UP and 73.6% in Bihar [6]. ORS treatment rates were low at 17.4% in UP, 36.7% in Gujarat and 22% in Bihar [6]; whereas treatment with zinc was negligible in all three states [7].

As can be seen, the demonstration projects were initiated by MI in the three states against this backdrop of high prevalence of child diarrhea, low care–seeking and treatment coverage. In addition, across all three states, ORS and zinc distribution for childhood diarrhea treatment was hampered by budgeting and procurement issues, and there was a lack of systematic health worker training to effectively



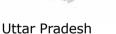




Figure 1. Map of intervention districts.

Table 2. Project area description

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Program aspect	Gujarat	Uttar Pradesh	Bihar
Donor	USF–BMGF/Teck	USF-BMGF	CIFF
Project name	Diarrhea Alleviation through Zinc and ORS Therapy (DAZT)	Diarrhea Alleviation through Zinc and ORS Therapy (DAZT)	Reducing Deaths from Diarrhea in the Indian State of Bihar
Year of initiation	2010	2010	2010
Year of completion	2014	2014	2015
Geographic coverage	6 demonstration districts 27 scale–up districts	12 demonstration districts	15 demonstration districts, 23 scale–up districts
Target population in the age group of 2–59 months (estimated based on Census of India 2011) [9]	5370014	4338314	13211546

USF – US Fund for UNICEF, BMGF – Bill and Melinda Gates Foundation, CIFF – Children's Investment Fund Foundation, DAZT – Diarrhea Alleviation through Zinc and ORS Treatment

manage childhood diarrhea cases based on revised national guidelines.

Key program strategies

The main strategy was to strengthen public sector capacity to manage childhood diarrhea using zinc and ORS at both facility and community levels. Key program components included:

- Building capacity of facility level health providers, and frontline health workers including integrated child development services (ICDS) workers,
- Extending service delivery to communities through frontline workers and at health facilities,
- Ensuring supplies of ORS and zinc at all levels,
- Providing supportive supervision to community health workers,
- Conducting monitoring and evaluation activities.

Capacity building of health providers

One of the objectives of the program was to ensure enhanced knowledge of service providers on zinc and ORS. This included enabling providers to prescribe zinc and ORS for treating childhood diarrhea and to undertake necessary counseling of caregivers for using these products. A formative research study was conducted in five demonstration districts of Bihar as a part of the program to better understand issues pertaining to knowledge, attitude and practices (KAP) prevalent in the community and among service providers regarding childhood diarrhea management [8]. The Formative study was largely based on qualitative research methods including in-depth interviews with 22 mothers of children under five years, 18 caregivers (grandmothers and adolescent sisters), 21 influencers (experienced mothers and respected community members), 32 block-level health officials (Lady Health Visitors, Block Health Educators, and Medical Officer In-charges), 20 CHWs, 8 doctors and 26 medical store attendants, along with focus group discussions (FGDs) with 20 mothers of

children under five years. The study findings reflect knowledge gaps among mothers and caregivers on causes and prevention of diarrhea. The caregivers and service providers found to have poor knowledge on use of zinc for child diarrhea treatment. The findings of this study in Bihar were also utilized in UP and Gujarat. One key gap identified in this qualitative research included knowledge of zinc use for the treatment of childhood diarrhea, and this finding informed the training curriculum for health providers. Specifically, the training curriculum and inter-personal communication (IPC) tools for increasing awareness among caregivers during interaction in one to one and smaller groups were designed for all three states and focused on zinc and ORS and improved case management of dehydration and other related complications. The training modules and methods were further developed for varying capacities of service providers at different levels, and included a training video CD in vernacular and pictorial job aids for conducting the trainings.

An 'NGO model' was utilized for the trainings such that professional trainers from select NGOs were hired to train health providers at district and sub-district levels. This was done since medical officers working in the public sector may not have the time or inclination to conduct a large number of trainings in addition to their routine work, and could not necessarily be expected to carry out trainings on such a large scale. However, medical officers were engaged as an expert resource during training sessions. As a result, 144 246 health providers were trained in the intervention districts of UP, Bihar and Gujarat. These providers included medical officers, auxiliary nurse midwives (ANMs), child development program officers (CDPOs), supervisors and anganwadi workers (AWWs) from ICDS and accredited social health activists (ASHAs). All trainings were completed during 2011–2012 except in four UP districts. Table 3 presents information on the number and types of participants trained in project districts of the three states. Pre and post-tests for participants and monitoring of training sessions were done to ensure quality of the training pro-

Tuble 5. Details of trained personner in 2011–2012			
CATEGORY OF PERSONNEL	GUJARAT (6 demonstration districts)	Uttar Pradesh (12 demonstration districts)	Bihar (15 demonstration districts)
District-level officials, medical officers and CDPOs	673	1736	1757
Block-level health supervisors, ANMs and ICDS supervisors	3547	7079	6864
ASHAs and AWWs	20198	57632	44 760
Total	24418	66447	53381

Table 3. Details of trained personnel in 2011–2012

CDPO – Child Development Project Officer, ANM – Auxiliary Nurse Midwife, ASHA – Accredited Social Health Activist, AWW – Anganwadi Worker, ICDS – Integrated Child Development Services

gram. Separate trainings were also conducted for assistant research officers (AROs) and data entry operators (DEOs) in order to improve their understanding on reporting childhood diarrhea cases.

Extending service delivery to communities

Prior to this program, childhood diarrhea management was predominantly carried out at the facility–level and CHWs were largely restricted to conducting community mobilization work.

One of the major objectives of the program was to enhance the use of zinc and ORS in the public sector for childhood diarrhea treatment. To achieve this, community level health workers including Accredited Social Health Activists (ASHAs) that work for the health department, and Anganwadi Workers (AWWs) that work for the department of woman and child development were involved in the program as service providers to increase public sector care seeking practices. During the program, ASHAs and AWWs were trained and supplied with zinc and ORS to manage diarrhea cases in communities, in addition to facility-based programs. The roles of CHWs included managing simple cases of diarrhea with ORS and zinc, identifying cases of moderate and severe dehydration for referral, and counseling of caregivers on appropriate diarrhea treatment and feeding practices during illness episodes. Thus, in the three states, service was delivered through a network of 66418 ASHAs, 75685 AWWs, 9516 health sub centers (HSCs), 918 primary health centers/community health centers (PHCs/CHCs) and 44 district-level hospitals in 33 demonstration districts.

Ensuring available supplies of ORS and zinc

Ensuring adequate and timely supplies of zinc and ORS was one of the major project strategies, which, along with supply chain management, are essential for ensuring continuous availability of zinc and ORS across all levels of the public health system.

In the beginning, MI introduced initial supplies in the form of combi–packs of zinc and ORS in 10 of the 15 demon-

stration districts of Bihar, 4 of the 6 districts of Gujarat and 8 of the 12 districts of UP. A total of 3157750 combi-packs were distributed. These combi-packs contained 14 tablets of taste-masked dispersible zinc (20 mg each), 2 packets of ORS, one measuring cup and an instruction leaflet. An additional 600 000 zinc tablets were distributed in the remaining 2 districts of Gujarat to be co-packaged with ORS supplies from the Gujarat government. Subsequently, in all the three states, MI facilitated incorporation of budgets under the National Health Mission (NHM) Project Implementation Plan (PIP) for procurement of ORS and zinc. After the first year, the government, in all three states, procured supplies. In Bihar, the state government procured and distributed zinc syrup for the treatment of childhood diarrhea. MI assisted the states to improve forecasting of zinc and ORS demand in order to strengthen procurement based on the child population estimates, diarrhea incidence, and care-seeking rates. It was ensured that states have rate contracts for zinc and ORS in place.

Providing supportive supervision to CHWs

CHWs require continuous support and guidance to sustain their knowledge levels in order to effectively manage diarrhea cases. To this end, a mechanism of supportive supervision was envisaged through a network of supportive supervisors at the sub-district level. A 'partnership model' was followed in UP and Gujarat, where supportive supervision was implemented in partnership with NGOs having a state-level presence, whereas in Bihar this support was provided using the existing cadre of government functionaries at PHCs called Block Community Mobilizers (BCMs). Supportive supervisors visited CHWs and provided oneon-one support to them and interacted with caregivers to understand their level of adherence to zinc treatment. In addition, they also addressed gaps in CHW capacities during group meetings. Supportive supervisors were provided with a checklist to be completed during supportive supervision visits in order to identify existing knowledge gaps. This checklist captured data on CHW knowledge, skills and availability of supplies.

During each visit, a supportive supervisor was expected to meet at least three field workers and one or two caregivers

who had visited CHWs with sick children. In the three states the number of ANM, ASHA, AWWs and caregivers reached through supportive supervision visits is shown in **Table 4**.

The sites visited for supportive supervision were planned each month and priority was accorded to poor performing frontline workers. The findings from supportive supervision visits were used to give one-to-one feedback as well as group feedback during monthly meetings with the frontline workers. Data was analyzed and findings were shared at national, state and district levels to understand program issues and to suggest mid-course corrective actions.

Conducting monitoring and evaluation activities

A Health Management Information System (HMIS) exists in the public health system for all three states in order to report on public health service delivery. However, HMIS captures data reported by ANMs at health sub–centre and above facilities but do not have a formal reporting tools for CHWs who were also involved in service provision under the project. Hence simple pictorial formats were developed to facilitate childhood diarrhea reporting by semi–literate CHWs. In addition, HMIS did not include indicators to track progress of key program aspects, such as dehydration levels and the number of diarrhea cases treated with both zinc and ORS. Therefore, a project reporting mechanism was developed to effectively track performance from all service delivery points, including CHWs using pictorial formats.

Trainings were provided to health care providers at all service delivery levels, including the CHWs who received close support through the supportive supervision mechanism previously described. A large number of cases were reported through this system from the beginning of the project in all three states. The Government of Bihar has involved CHWs for service delivery in the scale–up districts and has also introduced simple pictorial reporting tools based on the utility of this program reporting mechanism.

In Bihar, the government has added the following new HMIS indicators in that state:

• Number of cases of childhood diarrhea with no dehydration,

- Number of cases of childhood diarrhea with some dehydration,
- Number of cases of childhood diarrhea with severe dehydration,
- Number of cases of childhood diarrhea treated with both zinc and ORS,
- Number of cases of childhood diarrhea referred,
- Number of ASHAs reported ORS stock–out (lack of ORS availability),
- Number of ASHAs reported zinc stock–out (lack of zinc availability).

Currently the program is attempting to streamline and sustain the government HMIS reporting. In addition to reporting, data collected under supportive supervision and research studies also contributed to overall program monitoring in order to understand its progress and to take corrective actions as required. Program evaluation studies planned under this program were conducted by The Johns Hopkins School of Public Health (JHSPH) and results are reported elsewhere [10].

KEY ACHIEVEMENTS AND LESSONS LEARNED

This section describes key achievements and lessons learned from the programs in three states.

Ensuring regular availability of zinc and ORS supplies is critical for program performance and needs sustained efforts

Regular supplies increase diarrhea cases appropriately treated. Regular availability of zinc and ORS in the public sector is critical for the treatment of diarrhea cases with both zinc and ORS. Program data report that 593 030 childhood diarrhea cases received treatment in 6 demonstration districts of Gujarat between November 2011 and September 2014. More than 99% of these cases were treated with both zinc and ORS. In 12 demonstration districts of UP, 907 295 diarrhea cases reportedly received treatment between December 2011 and September 2014, and 86% of these cases were treated with both zinc and ORS. In Bihar, 1796 563 cases were reported to have received treatment in 15 demonstration districts between August 2011

Table 4. Total ANM, ASHA, AWW and caregivers visited during supportive supervision visits

ANM, ASHA, AWW and caregivers	GUJARAT (MAY 2013–SEPTEMBER 2014)	Uttar Pradesh (May 2013–September 2014)	BIHAR (DECEMBER 2011–SEPTEMBER 2014)
ANM	3648	2476	6252
ASHA	5500	8578	6237
AWW	5432	7631	6070
Caregivers	12579	9142	21984

ANM Auxiliary Nurse Midwife, ASHA - Accredited Social Health Activist, AWW - Anganwadi Worker

and September 2014, and 77% were treated with both zinc and ORS. Importantly, public sector service providers in intervention districts reported only those cases of childhood diarrhea that were provided with any treatment and cases not given treatment were not reported. In Gujarat, the higher percentage of childhood diarrhea cases treated with both zinc and ORS was largely due to the uninterrupted availability of zinc and ORS in that state compared to UP and Bihar that had supply interruptions (**Table 5**). A baseline study on caregiver' knowledge, attitude and practice on the use of zinc and ORS for childhood diarrhea in Bihar also reflects that availability of zinc and ORS with service providers is one of the reasons that prevents treatment seeking by caregivers for childhood diarrhea from such service providers [11].

These findings suggest that availability of regular supplies of zinc and ORS helps in treating a higher percentage of diarrhea cases with both zinc and ORS.

Ensuring regular supplies needs sustained efforts. The maintenance of regular zinc and ORS availability at different service delivery points has proved a challenge in the public sector, and particularly in states with relatively poor governance. In Bihar, supply audit studies were periodically conducted to assess zinc and ORS availability among CHWs. The supply audits indicated that there were no stock-outs in the first six months of supply distribution but thereafter 28% of ASHAs on average experienced stock-outs of both zinc and ORS between June 2012 and February 2014. After April 2014, there was a zinc stock-out at most service delivery points due to expiry of existing zinc syrup and other challenges faced by the state during the process of ensuring new procurement mechanisms. Similarly, in UP, ORS was unavailable at many of the services delivery points at different time periods between November 2013 and October 2014 due to procurement challenges.

MI and other development partners made sustained efforts to restore supplies in both Bihar and UP, such as through

advocacy for placement of procurement orders, providing technical support for accurate demand forecasting, advising on product specifications, and providing close support in supply distribution to service delivery points. Gujarat already had an improved supply chain mechanism that resulted in fewer ASHAs experiencing zinc and ORS stockouts (**Table 5**).

Indeed, ensuring regular supplies is one of the biggest challenges in the public health system not only in India but across the countries for treating childhood diarrhea with both zinc and ORS [12]. The important gaps that need to be addressed to ensure regular zinc and ORS availability include:

- Lack of knowledge among program managers in the public health system for forecasting the required quantity of drugs: In general, public sector supplies are procured without accurate demand calculations and therefore training and technical support for proper forecasting is important for procuring the adequate supply quantities [13].
- Complicated and time–consuming procurement processes: procurement is carried–out by the state government, for which getting the information on quantity required from various levels, placing procurement orders, testing drug quality and appropriate distribution is cumbersome and time–taking. Recognizing this problem, some of the states have engaged a dedicated corporation for their drug procurement and distribution. However, in some states such corporations are either newly established or not fully operational. Therefore technical support provided at different procurement stages could facilitate the process until these procurement corporations become fully functional.
- Lack of proper warehousing facilities at district and sub–district levels: Due to lack of proper storage facilities the districts and blocks (sub–districts) are

DISTRICT		Total number of child diarrhea cases brought to public sector for care and received any treatment		Child diarrhea cases seen in the public sector and treated with both zinc and ORS (%)
Gujarat‡	3	593 030	590552	99
Uttar Pradesh§	48	907295	778970	86
Bihar¶	28#	1796563	1 374 869	77

ORS – oral rehydration salts

*Stock out - lack of zinc/ORS availability.

†Childhood diarrhea cases treated with zinc and ORS are based on program reports. Gujarat cases refer to November 2011–September 2014; Bihar refers to August 2011–September 2014; UP refers to December 2011–September 2014.

‡Gujarat stock-out from May 2013-September 2014 is based on supportive supervision data.

§UP stock–out from May 2013–September 2014 is based on supportive supervision data.

[Bihar stock-out is based on supply audits conducted in January 2012, June 2012, October 2012, March 2013 and February 2014.

#After March 2014 there was zinc stock out with most of the service providers.

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unable to store supplies required for replenishing unanticipated stock-outs [14].

• Lack of an effective mechanism of tracking availability of supplies with CHWs and timely replenishment of stocks at service delivery points in the case of stock outs: The HMIS and drugs logistic management system (DLMS) does not track CHW supply availability, which is a major impediment for replenishing CHW stocks [15].

Regular supplies promotes caregiver confidence in CHWs and public health sector

Lack of available zinc and ORS weakens caregiver trust and reliance in the quality of public health care services, which adversely affects care—seeking at the public sector. A recent study [16] on care—seeking for childhood diarrhea and acceptance of CHWs as credible service providers in the demonstration districts in Bihar, found reduced trust among caregivers on the quality of care and services provided by CHWs, as a result of lack of zinc and ORS availability with them. In public health sector, frequent stock—outs also weaken the confidence of CHWs to provide treatment of child diarrhea. Similar findings were also observed in a study on health care reforms involving the introduction of user fees and drug revolving funds and their influence on health workers' behavior in Nigeria [17].

These results indicate the importance of regular zinc and ORS availability for increased public sector care seeking by improving the credibility of CHWs among caregivers and boosting confidence of the CHWs to act as well–equipped service providers.

Quality capacity building activities ensures sustained knowledge and skills of the health functionaries

A large number of health providers were trained in the program as previously described. These trainings were conducted with the help of external trainers who were supported technically by government medical officers, which facilitated the completion of trainings within the stipulated short timeline and with quality assurance. Though baseline data on CHW knowledge level is not available, data collected during supportive supervision visits provide information on knowledge levels of CHWs. During supportive supervision visits, information on CHW knowledge and capacity was collected using a checklist by block community mobilizers (BCMs) in Bihar and by NGO partners in Gujarat and UP. In Bihar nearly 100 BCMs placed at block level in 10 districts undertook a maximum of four supportive supervision visits each month. In Gujarat and UP, 20 and 27 supportive supervisors, respectively, undertook field visits for approximately 20 days in each month. During each visit, a supportive supervisor was expected to meet and collect data from at least three field workers (1 ANM, 1 ASHA and 1 AWW) and to meet with one or two caregivers who attended CHW services. These data were analyzed on a monthly basis and generally showed sustained CHW knowledge and skills, which indicates the good quality of training provided under the program (Table 6). Table 6 highlights ASHA awareness level regarding the definition of diarrhea (three or more watery stool within 24 hours) was either sustained or improved. Similarly, there was sustained or increased ASHA awareness about the age-wise correct dosage of zinc across the three states (Table 7). An end-line evaluation study of caregivers' knowledge, attitude and practice on the use of zinc and ORS for childhood diarrhea, carried out in 11 blocks of five districts of Gujarat, where trainings were conducted using similar methods that were adopted under the DAZT program districts, also show a high and sustained knowledge of ASHA on identification of childhood diarrhea and its management protocols [18].

Involvement of CHWs strengthens service delivery and performance reporting

Enhances percentage of cases treated at community lev-el. A key program strategy was to involve CHWs in the

Table 6. ASHA knowledge of diarrhea definition

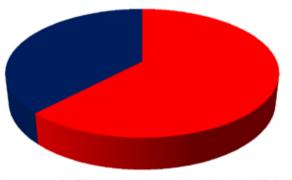
DISTRICT	May 2013		November 2013		May/June 2014		September 2014	
	Number of ASHAs visited	ASHA knows definition of diarrhea (%)	Number of ASHAs visited	ASHA knows definition of diarrhea (%)	Number of ASHAs visited	ASHA knows definition of diarrhea (%)	Number of ASHAs visited	ASHA knows definition of diarrhea (%)
Gujarat	315	94	208	99	307	95	176	90
Uttar Pradesh	366	51	443	81	552	81	585	94
Bihar*	211	88	196	94	51	90	141	89

ASHA - Accredited Social Health Activist

*In Bihar supportive supervision data shown in May/June 2014 column refers to data collected in June 2014. The activity was halted for about two to three months (April to mid–June 2014) to make necessary changes like role out of new formats, training of supervisors etc as a result number of ASHAs visited are less. For other states the data pertains to May 2014.

management of child diarrhea cases and to report program performance. Availability of services increased at the community level by involving CHWs in service delivery. In Bihar, 62% of non–facility cases seen by ANMs and CHWs were treated and reported by CHWs. This indicates better availability of services and easy access by caregivers near their homes. A similar pattern of CHW treatment and reporting was also found in UP and Gujarat (**Figure 2**). Evalutation of DAZT program in Gujarat reflects increased coverage of diarrhoea treatment by CHWs [10].

Improves tracking program performance and increases reporting of child diarrhea cases. Along with service de-



% cases reported by CHWs & cases reported by Auxiliary Nurse Midwife (ANM)

Figure 2. Proportion of cases treated and reported by community health workers (CHW) and auxiliary nurse midwives (ANM) in Bihar, May 2013. livery, CHWs were also involved and trained for performance reporting. The public health system has traditionally focused on facility–based data and reporting. In this program, CHWs were also involved in reporting in order to track the treatment of cases at the community level. As previously described, a simple pictorial format was developed to facilitate CHW reporting and CHW capacities for reporting were reinforced through supportive supervision visits. The number of reported cases increased after involving CHWs in the reporting process. **Figure 3** shows the increased number of childhood diarrhea cases in Bihar both before and after CHW reports were integrated into HMIS in that state.

Reporting by CHWs however requires further strengthening. Reporting completeness exercises conducted in the three states indicated that only 41% of ASHAs in Bihar (May 2013), 57% in UP (July 2013) and 82% in Gujarat (June 2013) were able to report cases using the standard form, and the remaining were not able to submit the report. CHW report submission can be further improved by streamlining the reporting mechanism, ensuring availability of reporting tools and close supervision to enhance their capacity on case reporting. A review of integrated community case managemnt in sub Sahara African countries also highlights that involvemnt of reporting by CHWs can strngthen HIMS, if CHWs are provided simple reporting tools and have a few selective indicators to report [19].

Enhances caregiver access and reach of public health services for childhood diarrhea management Involv-

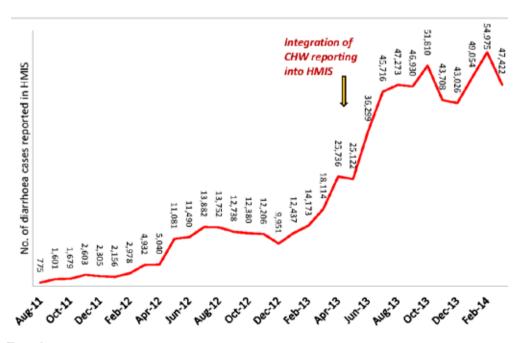


Figure 3. Diarrhea cases reported in 15 demonstration districts of Bihar before and after integrating the community health worker (CHW) reporting system into Health Management Information System (HMIS).

Table 7. ASHA	knowledge	about a	ge–wise	zinc doses

DISTRICT	May 2013		November 2013	}	May/June 2014	ļ.	September 201	4
	Number of ASHA visited	ASHA knows age wise dose of zinc (%)		ASHA knows age wise dose of zinc (%)	Number of ASHA visited	ASHA knows age wise dose of zinc	Number of ASHA visited	ASHA knows age wise dose of zinc (%)
Gujarat	315	87	208	92	307	91	176	96
Uttar Pradesh	366	52	443	69	552	54	585	71
Bihar*	211	86	196	95	51	86	141	83

ASHA - Accredited Social Health Activist

*In Bihar supportive supervision data shown in May/June 2014 column refers to data collected in June 2014. The activity was halted for about two to three months (April to mid–June 2014) to make necessary changes like role out of new formats, training of supervisors etc as a result number of ASHAs visited are less. For the other states the data pertains to May 2014.

ing CHWs in service provision for childhood diarrhea management helps increase caregivers access to services and the reach of the public health system. A rapid assessment study conducted by MI in Gujarat and UP suggested that caregivers prefer receiving free–of–cost services closer to home from CHWs [20]. Making the community aware about the availability of zinc and ORS with CHWs, coupled with strong CHW skills and training in the management of child diarrhea, can further enhance the acceptability of CHWs by the community. This in turn will help increase zinc and ORS coverage through the public sector.

Probably a component of behaviour change communication as a part of program strategies would have contributed to increase in caregivers' awareness thereby resulting in greater demand for zinc and ORS for management of childhood diarrhea.

Continuous engagement with government and sharing early evidences of program performance facilitated government decision-making for scale-up

In order to ensure government ownership from the program outset, attempts were made to continously engage the government at all levels. At the start of the program, Memoranda of Understanding (MOUs) were signed with the state governments of Gujarat and Bihar. The program was also reviewed regularly at the block, district and state levels, which helped strengthen service delivery. In addition, information on program performance was also shared regularly with districts and state level authorities. This continuous engagement with the government and regular sharing of progress achieved has been important for ensuring government ownership, and has paved the path towards the program scale–up.

For the purpose of scale–up, the program have focused since its outset in generating evidence of program performance, ensuring buy–in from the government on program strategies, and enhancing capacity of government functionaries. Generating early evidence on effectiveness and regularly sharing these updates with government counterparts has facilitated the government's decisions for scale–up of specific program strategies. Despite the challenges in procurement, affecting the program achievements, in UP and Bihar the following strategies have been scaled–up by all the three states to facilitate program expansion across districts [21]:

- CHW involvement in service delivery is now implemented across the entire states of UP, Bihar and Gujarat
- Estimation of zinc and ORS stocks and supply provision to all service delivery points
- Regular reporting mechanisms of cases through the HMIS in Bihar
- Service provider trainings in childhood diarrhea treatment using ORS and zinc

The state governments have earmarked budgets for the procurement of zinc and ORS across districts in order to scale–up program strategies. Bihar, Gujarat and UP governments have incorporated these program activities in their annual plans and have submitted budget proposals to the Government of India for implementation across all districts. The Government of India has approved these proposed budgets for 2012–2013 and subsequent years [22].

Regular technical support and evidence– based policy advocacy leads to policy changes and release of implementation guidelines

The advocacy efforts undertaken and technical support provided by MI and other development partners at national levels have resulted in the development of operational guidelines by the Ministry of Health and Family Welfare, Government of India [23]. These guidelines include strategies used in the demonstration districts that will help facilitate roll–out of program strategies across all states of India. The advocacy efforts of MI and other partners have also facilitated the following policy changes that will enhance the availability of zinc supply in India:

• Zinc specifications included in the Indian pharmacopeia: Due to this change more Indian pharmaceutical companies can start production of therapeutic zinc [24]

- Zinc included in the essential drug list: The Government of India has included zinc in the list of essential medicines [25]. This will help to ensure zinc availability at service delivery points in the public health sector
- Indicators on zinc usage included in large–scale national surveys (eg, Annual Health Survey of India) [26] and District Level Health Survey–4 [27]): This will help the government track the use of zinc for child diarrhea management at the national and sub– national levels

Limitations

Information on certain aspects of program has been collected only during the implementation of the projects across the three states and detailed information on these aspects, like stock out of zinc and ORS, reporting of the cases treated with zinc and ORS, cases of childhood diarrhea treated by CHWs, knowledge level of CHWs on management of childhood diarrhea is not available prior to the initiation of the project implementation. Since data collected during the evaluation studies is being published as a separate paper on evaluation findings in this same issue of the journal, hence evaluation data has not been used in this paper. This paper is largely based on program monitoring and data collected through government functionaries which may have some limitations.

DISCUSSION AND CONCLUSIONS

This program shows that management of childhood diarrhea using zinc as an adjuvant to ORS when implemented through CHWs in addition to improved services provided through public health facilities, leads to increased service accessibility by the community and increased credibility of the public health system resulting in increased coverage [10].

Prior to the initiation of these projects, the use of zinc and ORS for management of childhood diarrhea was not a focused intervention under the government system in the program states. The exposure of government functionaries on use of zinc and ORS for management of childhood diarrhea was therefore limited and the overall use of zinc was low in all the three states. Some of the critical strategies which were implemented across the states like facilitating procurement of supplies by government, capacity building of service providers and managers across cadres, introduction of simple reporting tools for CHWs, program monitoring and review helped in improving knowledge of service providers and increasing uptake of zinc and ORS. The professional trainings imparted through the program improve CHW capacities and enhanced their skills and knowledge thereby increasing their acceptance in the community as health service providers. However, such outcomes are possible only if there is government ownership of the program, quality training of health service providers, timely and adequate procurement of quality products, timely distribution, an efficient tracking mechanism to identify stock–outs for replenishment, routine monitoring and critical reviews at all levels regarding quality of training provided to service providers.

The strategies adopted under the program have resulted in increased utilization of public health services and use of zinc and ORS for childhood diarrhea treatment. These program outcomes could have further increased if these were supported by activities to generate community awareness on use of zinc and ORS for childhood diarrhea and its availability at public health providers. However, the program did not have any Behaviour Change Communication (BCC) component, other than interpersonal communication, as a part of program strategies. Inclusion of behaviour change communication strategies would have contributed to increase in caregivers' awareness thereby resulting in greater demand for zinc and ORS for management of childhood diarrhea. This has also been substantiated by an evaluation study on caregiver awareness generation activities carried out in 11 blocks of five districts of Gujarat which reflects increased coverage of zinc and ORS for childhood diarrhea at public sector as a result of caregiver awareness generation activities [18].

This program experiences reflect that it is feasible and viable to introduce and scale-up therapeutic zinc supplementation as an adjuvant to ORS in the management of childhood diarrhea through the public sector. Some of the components which are likely to be sustained beyond the program period under the donor funded childhood dairhoea management program in the three states include knowledge level of service providers, engagement of community health workers for service delivery and reporting through HMIS. It is because some of these components have got included in the government program implementation plan and Government of India has developed and rolled out operational guidelines for childhood diarrhea management and has launched the programs such as India Action Plan for Pneumonia and Diarrhea (IAPPD) and Intensified Diarrhea Control Fortnight (IDCF) which has given significant impetus and brought renewed focus on Childhood diarrhea management.

Demonstration projects like the one reported in this paper, play a critical role in generating early evidence to influence government decisions for scale–up of programs and accelerate necessary policy changes. Acknowledgments: This program was implemented in partnership with the governments of the Indian states of Gujarat, UP and Bihar and was funded by The Bill and Melinda Gates Foundation through the US Fund for UNICEF and the Children's Investment Fund Foundation (CIFF). We acknowledge the support of the government, our donors, partners, communities and colleagues at MI India, Asia region and headquarters. We would also like to recognize the constant guidance received from the Regional Director, MI throughout the project duration.

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Ethical approval: The paper does not violate ethical norms of anyone concern in the program. The ethical norms have been followed, confidentiality of the healthcare providers who are the main source of information, have been maintained.

Authorship declaration: SD and RR have managed the program and SK has led the monitoring and research of the program at national level. SK, SD and RR have provided the ideas to conceptualize and prepare the paper. SK compiled and analyzed the data, created evidences and in consultation with SD and RR compiled the lessons. SK prepared the manuscript and finalized with RR and SD

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 four years; and no other relationships or activities that could appear to have influenced the submitted work.

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Global and regional estimates of COPD prevalence: Systematic review and meta–analysis

Davies Adeloye, Stephen Chua, Chinwei Lee, Catriona Basquill, Angeliki Papana, Evropi Theodoratou, Harish Nair, Danijela Gasevic, Devi Sridhar, Harry Campbell, Kit Yee Chan, Aziz Sheikh, Igor Rudan; Global Health Epidemiology Reference Group (GHERG)

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Professor Igor Rudan, MD, DSc, PhD, MPH, HonMFPH Chair in International Health and Molecular Medicine Joint Director, Centre for Global Health Research and WHO Collaborating Centre for Population Health Research and Training Director of Research, The Usher Institute for Population Health Sciences and Informatics University of Edinburgh Teviot Place, Edinburgh EH8 9AG Scotland, UK Igor.Rudan@ed.ac.uk **Background** The burden of chronic obstructive pulmonary disease (COPD) across many world regions is high. We aim to estimate COPD prevalence and number of disease cases for the years 1990 and 2010 across world regions based on the best available evidence in publicly accessible scientific databases.

Methods We conducted a systematic search of Medline, EMBASE and Global Health for original, population–based studies providing spirometry–based prevalence rates of COPD across the world from January 1990 to December 2014. Random effects meta–analysis was conducted on extracted crude prevalence rates of COPD, with overall summaries of the meta–estimates (and confidence intervals) reported separately for World Health Organization (WHO) regions, the World Bank's income categories and settings (urban and rural). We developed a meta–regression epidemiological model that we used to estimate the prevalence of COPD in people aged 30 years or more.

Findings Our search returned 37472 publications. A total of 123 studies based on a spirometry-defined prevalence were retained for the review. From the meta-regression epidemiological model, we estimated about 227.3 million COPD cases in the year 1990 among people aged 30 years or more, corresponding to a global prevalence of 10.7% (95%) confidence interval (CI) 7.3%–14.0%) in this age group. The number of COPD cases increased to 384 million in 2010, with a global prevalence of 11.7% (8.4%-15.0%). This increase of 68.9% was mainly driven by global demographic changes. Across WHO regions, the highest prevalence was estimated in the Americas (13.3% in 1990 and 15.2% in 2010), and the lowest in South East Asia (7.9% in 1990 and 9.7% in 2010). The percentage increase in COPD cases between 1990 and 2010 was the highest in the Eastern Mediterranean region (118.7%), followed by the African region (102.1%), while the European region recorded the lowest increase (22.5%). In 1990, we estimated about 120.9 million COPD cases among urban dwellers (prevalence of 13.2%) and 106.3 million cases among rural dwellers (prevalence of 8.8%). In 2010, there were more than 230 million COPD cases among urban dwellers (prevalence of 13.6%) and 153.7 million among rural dwellers (prevalence of 9.7%). The overall prevalence in men aged 30 years or more was 14.3% (95% CI 13.3%-15.3%) compared to 7.6% (95% CI 7.0%-8.2%) in women.

Conclusions Our findings suggest a high and growing prevalence of COPD, both globally and regionally. There is a paucity of studies in Africa, South East Asia and the Eastern Mediterranean region. There is a need for governments, policy makers and international organizations to consider strengthening collaborations to address COPD globally.

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In a follow-up to the 2011 United Nations (UN) high level political declaration on non-communicable diseases (NCDs) [1], the World Health Assembly, in 2012, endorsed a new health goal (the "25 by 25 goal"), which focuses on reduction of premature deaths from COPD and other NCDs by 25% by the year 2025 [2]. Despite this initiative, experts have reported that COPD remains a growing [3], but neglected global epidemic [4]. The World Health Organization (WHO) estimated that there were about 62 million people with moderate to severe COPD in 2002, with the total number of COPD cases predicted to increase to about 200 million in 2010 [5,6]. According to the 2010 Global Burden of Disease (GBD) study, COPD was responsible for about 5% of global disability-adjusted life years - DALYs (76.7 million) - and 5% of total deaths (2.9 million) [7,8]. COPD is currently rated the fourth most common specific cause of death globally and predicted to be the third by 2030, in the absence of interventions that address the risks - especially tobacco smoking, exposures to combustion products of biomass fuels and environmental pollution [9,10].

The burden of COPD has been reported to be high in some high-income countries (HIC), particularly due to high prevalence of smoking in these settings [11]. For example, between years 2000 and 2010, about 4%-10% of adults were diagnosed with non-reversible and progressive airway obstruction (a basic feature of COPD) in populationbased surveys across many European countries, with smoking indicated as a major risk [12]. The WHO has estimated that in many HIC up to 73% of COPD deaths are related to tobacco smoking [6]. The European Union (EU) reported that the direct cost from COPD was over 38.6 billion Euros in 2005, representing about 3% of total health care expenditure [13,14]. In the United States (US), over 2.7 million adults were estimated to have COPD in 2011, with about 135000 deaths reported [15]. In 2010, the US government spent nearly US\$ 49.9 billion on COPD, including 29.5 billion spent on direct health care, 8.0 billion on indirect morbidity and 12.4 billion on indirect mortality costs, respectively [15].

Meanwhile, it has been estimated that despite a high prevalence of COPD in some HIC, 90% of COPD deaths still occur in low– and middle–income countries (LMIC) [4] and 40% of these deaths are attributable to smoking [6]. The burden in LMIC has been comparatively high owing to relatively low COPD awareness, challenges with COPD diagnosis and increased exposures to additional risk factors, especially combustion products of biomass fuels [16]. Salvi and colleagues reported that about 3 billion people globally are exposed to smoke from biomass fuel, compared to 1 billion people who smoke tobacco globally [17]. In many developing countries COPD is neglected by governments, physicians, experts and the pharmaceutical industry, although it's been identified as an important public health problem [4].

In the last two decades, the Burden of Obstructive Lung Disease (BOLD) initiative has been collecting country-specific data on the prevalence, risk factors and socioeconomic burden of COPD, using standardized and tested methods for conducting COPD surveys in the general population [18]. This is expected to provide governments of many nations with country-specific evidence on which to develop policy on COPD prevention and management [18]. As noted above, this initiative is yet to take a full effect in many LMIC [19]. In addition, spirometry (the gold standard for COPD diagnosis) is not widely available in many LMIC [16]. Even when it is there, professionals in LMIC are often not being trained properly on how to use spirometers or interpret spirometry results. There is concern that COPD burden has been underestimated, owing to over-reliance on doctor's diagnosis, with many diagnoses not being based on spirometry and international diagnostic guidelines [20]. The lack of routine COPD data collation and effective health information management system in many LMIC also implies that these settings could have been grossly underrepresented in global burden of COPD estimates [11].

Some global and regional estimates of COPD burden have been published [1,21–23]. However, despite the fact that COPD is now prevalent in both HIC and LMIC, experts have raised concerns that reliable estimates of COPD prevalence are still few in many parts of the world. Moreover, many of the estimates are based on varying definitions and diagnostic criteria of COPD [9]. Also, some of the current estimates were reported before the BOLD surveys in several countries, thereby failing to account for the additional spirometry-based epidemiological data from the BOLD surveys. There is a need for a revised and updated estimate of COPD prevalence across world regions. We conducted a systematic review of COPD prevalence based on spirometry data across world regions. Our aim was to provide global and regional prevalence rates of COPD that could facilitate adequate policy response in these regions.

METHODS

Search strategy and selection criteria

After identifying relevant Medical Subject Headings (MeSH), we conducted a systematic search of Medline, EM-BASE and Global Health for studies estimating the prevalence of COPD globally from January 1990 to December 2014. We also searched Google Scholar for unpublished studies. Reference lists of retained publications were further hand-searched for studies omitted in our initial searches (see search terms in Tables s1–3 in **Online Supplementary Document**). We included original population-based (cohort or crosssectional) studies conducted worldwide. The retained studies provided estimates of the prevalence and number of cases of COPD and/or relevant population-based information from which COPD prevalence could be estimated. We excluded studies that had unclear study designs and methodologies, conducted before 1990, on non-human subjects, and that were reviews, viewpoints or editorials. No language restrictions were applied.

Case definitions

Based on an understanding of the diagnosis of COPD as reported by respiratory physicians, we included only studies that were based on spirometry, as these have been shown to be consistent with the diagnosis of COPD worldwide [24,25]. However, it is important to note that experts may still not fully agree on the spirometry-based definition that best defines COPD [26]. In 2001, the Global initiative on Obstructive Lung Disease (GOLD) recommended using the ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) that is less than 70% in the diagnosis of COPD (FEV₁/FVC<70%) [25,27]. This diagnostic criterion was also endorsed by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2004 [28]. It has been acknowledged that this criterion is simple and independent of reference equations [26]. However, the use of a fixed FEV,/FVC ratio has been debated from a number of perspectives [29–32], which we summarized in the discussion (see later). For the current study, we selected studies that used case definitions for COPD as shown in detail in Table 1.

Data extraction, synthesis of results and analysis

All extracted data were stored in Microsoft Excel file format. A parallel search and extraction was conducted by three independent reviewers (SC, CL and CB). Any disagreement between the three reviewers over article inclusion, exclusion and/or data extraction for the current study was resolved through re-review of their work and agreement between their two supervisors (DA and IR). We did not calculate Kappa statistics for the agreement between all reviewers because it was not amenable to straightforward computation and interpretation in this two-stage extraction process, which was based on a mix of independent review and collaborative re-review. Also, we did not make any attempts to contact the authors of studies that were rejected based on unclear reporting. Data were abstracted systematically on sample size, mean age, number of COPD cases, and the respective age- and sex- specific prevalence rates. These were classified into WHO regions, the World Bank's income categories, and study setting (urban, rural or mixed). For studies conducted on the same study site, pop
 Table 1. Basic characteristics of the studies retained for the analyses (a total of 140 study sites from 123 studies)

Characteristics	STUDY SITES
WHO regions:	
AFRO	6
AMRO	15
EMRO	7
EURO	64
SEARO	6
WPRO	42
Income category:	
High	87
Low and middle	53
Settings:	
Mixed*	52
Urban	63
Rural	25
Study period:	
1990–1999	24
2000–2009	94
2010-present	22
COPD case definitions:	
FEV ₁ /FVC<70%	130
FEV ₁ /FVC <lln< td=""><td>8</td></lln<>	8
FEV ₁ /FVC<75%	1
FEV₁/FVC≤65%	1

COPD – chronic obstructive pulmonary disease, FEV – forced expiratory volume, FVC – forced vital capacity, LLN – lower limit of normal *Studies presenting a joint COPD estimate for urban and rural settings.

ulation or cohort, the first chronologically published study was selected, and all additional data from other studies were included in the selected paper. All extracted information from the retained studies is available in Table s4 in **Online Supplementary Document**.

A random effect meta–analysis (DerSimonian and Laird method) was conducted on extracted crude prevalence rates of COPD [33]. Overall summaries of the meta–estimates (and confidence intervals) were reported separately for the WHO regions, the World Bank's income categories, and study settings, all expressed as percentages.

We developed a meta-regression epidemiological model and applied this on crude prevalence rates of COPD. In this model, mean ages corresponding to each prevalence rate were plotted on the *x*-axis (independent variable) and crude prevalence rates were plotted on the *y*-axis (dependent variable). We accounted for variation in sample sizes from each data point and controlled for year of publication to generate estimates of COPD prevalence for the years 1990 and 2000, respectively. The best fit was then used in our model and the equation generated from the fitted line was applied to the respective midpoints of the United Nations (UN) 5-year age-group population estimates for the years 1990 and 2010, respectively (United Nations, 2013). This enabled us to determine the prevalence of COPD glob-

RESULTS

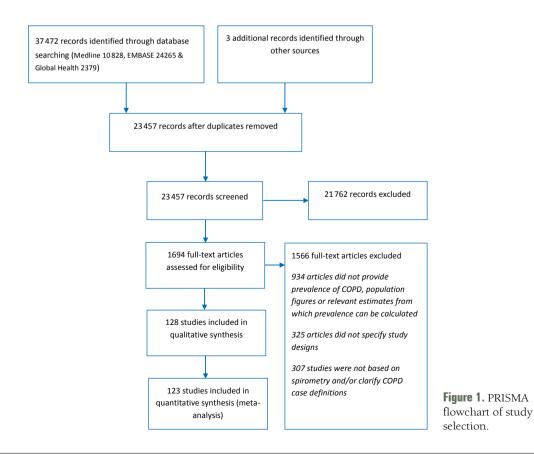
Systematic review

Our search returned 37472 publications: 10828 in Medline, 24265 in EMBASE and 2379 in Global Health. A further three studies were included from other sources (Google Scholar and hand-searching reference list of relevant publications). 23457 studies remained after removing duplicates. After screening titles for relevance (studies estimating the burden of COPD) 21762 studies were excluded. We therefore assessed 1694 full-text papers. After applying the quality criteria, 1566 studies were excluded. This is because 934 articles did not provide prevalence data on COPD, population figures or relevant estimates from which prevalence can be calculated; further 325 articles did not specify study designs; and 307 studies were not based on spirometry and/or clarify COPD case definitions. A total of 128 studies were retained for the review, with 123 providing quantitative data for a total of 140 study settings (see Figure 1 for the PRISMA flow diagram of study selection).

Study characteristics

The retained studies [23,26,35–155] were conducted across 140 locations spread across the six regions of the WHO (see Table s4 in **Online Supplementary Document**). European (EURO) and Western Pacific (WPRO) regions had the highest number of studies with 64 and 42 study sites, respectively. This was followed by the American region (AMRO) with 15 study sites. Eastern Mediterranean region (EMRO) had seven study sites, while the African region (AFRO) and South East Asia region (SEARO) each had six study sites (**Table 1**). Five studies were conducted in multiple sites. They included the BOLD study [40], European Community of Respiratory Health Survey (ECRHS) [113], the PLATINO study in Latin America [23] and two other studies in Europe [61,89].

A total of 52 countries were represented, with China contributing the largest number of studies (22 in total). The mean age across studies was 54.1 years, ranging from 32 to 74 years. The total population from all studies was 877 566. The COPD survey guidelines employed across selected studies included GOLD, ATS, ATS/ERS and the British Thoracic Society (BTS) (see Table s4 in **Online Supplementary Document**). However, COPD diagnosis was based on the diagnostic criterion of FEV₁/FVC<70% in 92.2% of all retained studies (see **Table 1** and Table s4 in **Online Supplementary Document** for detailed explanation of characteristics of selected studies).



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Meta-estimates from crude COPD prevalence rates

Forest plots were used to give a visual assessment of the pooled crude prevalence along with 95% confidence intervals of COPD by WHO regions, by study settings, and by the World Bank income category (**Figures 2-4**). We used the I²-statistic to evaluate heterogeneity in COPD prevalence between the retained studies. From the random effects meta–analysis, a prevalence of 11.4% (CI: 10.8%–12.0%) was estimated globally in people aged ≥30 years (**Figure 2**). The overall prevalence was higher among men (14.3%; CI: 13.3%–15.3%) than women (7.6%; CI: 7.0%–8.2%) (**Table 2**).

Among the WHO regions, AMRO region had the highest prevalence (14.1%; CI: 11.4%–16.7%), followed by EMRO (13.2%; CI: 8.8%–17.7%) and EURO (12.0%; CI: 10.7%–13.2%). AFRO had an estimated prevalence of 10.6% (CI: 6.1%–15.1%) and WPRO of 10.0% (CI: 9.0%–11.0%). SEARO had the lowest prevalence of 7.8% (CI: 5.3%–10.4%) (**Figure 2** and **Table 2**).

Across most settings, urban dwellers had higher COPD prevalence rates (13.2%; CI: 11.8%–14.7%) than rural populations (10.2%; 8.2%–12.2%) (**Figure 3** and **Table 2**). An analysis according to the World Bank's income categories revealed that the prevalence was higher in high–income countries (HIC): 12.0% (CI: 11.0%–13.0%), compared to 10.6% (CI: 9.5%–11.6%) in LMIC (**Figure 4** and **Table 2**).

Modelled estimates of COPD prevalence and number of cases

The initial meta-regression analysis showed a significant effect of mean age and the year of study on estimated

Table 2. Summary of pooled crude COPD prevalence from
selected studies (prevalence expressed in percentages for the
population aged 30 years or older)

	BOTH SEXES (95% CI)	Men (95% CI)	Women (95% CI)
World	11.4 (10.8–12.0)	14.3 (13.3–15.3)	7.6 (7.0–8.2)
WHO region:			
AFRO	10.6 (6.1–15.1)	15.1 (8.8–21.3)	8.0 (4.1–11.9)
AMRO	14.1 (11.4–16.7)	17.6 (14.6–20.6)	11.8 (9.7–13.9)
EMRO	13.2 (8.8–17.7)	15.3 (5.9–24.7)	6.0 (2.5–9.5)
EURO	12.0 (10.7–13.2)	13.7 (12.0–15.3)	7.6 (6.8–8.5)
SEARO	7.8 (5.3–10.4)	9.3 (4.7–13.9)	3.6 (2.4–4.9)
WPRO	10.0 (9.0–11.0)	14.4 (12.5–16.3)	6.4 (5.3–7.5)
Study setting:			
Mixed*	9.7 (8.9–10.5)	13.2 (11.8–14.6)	5.7 (5.3–6.2)
Urban	13.2 (11.8–14.7)	15.7 (13.7–17.7)	9.4 (8.3–10.6)
Rural	10.2 (8.2–12.2)	13.1 (8.5–17.7)	6.3 (4.4–8.2)
Income categor	y:		
High	12.0 (11.0–13.0)	14.3 (13.0–15.6)	8.1 (7.3–8.8)
Low and middle	10.6 (9.5–11.6)	14.5 (12.3–16.7)	6.5 (5.8–7.2)

COPD – chronic obstructive pulmonary disease, CI – confidence interval *Studies presenting a joint COPD estimate for urban and rural settings.

COPD prevalence rates. We therefore controlled for these effects in the model (**Figure 5** and **Table 3**) [34]. From the model based on meta–regression we estimated about 227.3 million COPD cases in the year 1990 among people aged 30 years or more, corresponding to the global prevalence of 10.7% (7.3%–14.0%) in this age group. However, the number increased to 384 million COPD cases in 2010, corresponding to the global prevalence of 11.7% (8.4%–15.0%). This is an increase of 68.9% and it is driven mainly by the global demographic changes over the 20–year period (**Table 4**).

Based on the UN percentage of people living in urban areas in 1990 (43.0%) and 2010 (51.6%) [156], we estimated the global population in these regions in those two years.

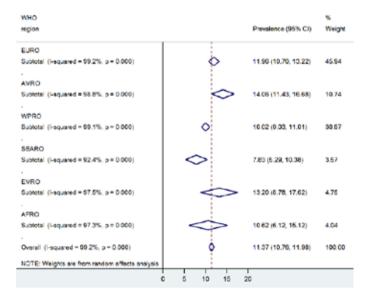


Figure 2. Overall pooled crude prevalence of COPD by WHO regions.

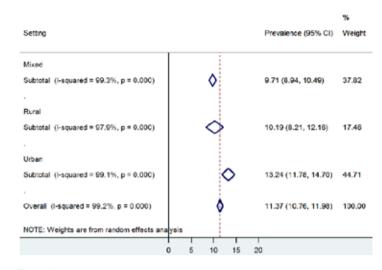


Figure 3. Overall pooled crude prevalence of COPD by study settings.

Table 3. Summary of meta-regression analysis

Prevalence	COEFFICIENT	SE		P > 1	95% CI LOWER	95% CI UPPER
Age	0.1662	0.0633	2.63	0.01	0.0410	0.2913
Year	0.0447	0.0923	0.48	0.629	-0.1377	0.2272
Constant	-87.1297	184.5720	-0.47	0.638	-452.1321	277.8727

CI – confidence interval

Our model revealed higher prevalence and number of COPD cases among urban dwellers. In 1990, we estimated about 120.9 million COPD cases among people aged 30 years or more, accounting for a prevalence of 13.2% (10.0%–16.4%). At the same time, rural dwellers had 106.3 million cases, accounting for a prevalence of 8.8% (6.5%–11.1%). By the year 2010, the number of COPD cases among urban dwellers rose to more than 230 million, accounting for a prevalence of 13.6% (11.2%–16.9%), and about 153.7 million cases among rural dwellers, accounting for a prevalence of 9.7% (7.6%–11.8%). The percentage of increase in COPD cases between 1990 and 2010 was higher among urban dwellers than among rural residents (90.5% vs 44.6%, respectively) (**Table 5**).

DISCUSSION

This study is among the first systematic attempts to estimate the prevalence of COPD across the world regions using spirometry–based data. The estimates presented here are based on the age range starting from 30 years, while many of the previous reviews were based on people aged 40 years or older. An appreciable prevalence of COPD has been reported in younger population groups, adding to uncertainties over the current epidemiological situation globally.

In the current study, we estimated a global prevalence of 10.7% (7.3%–14.0%) in 1990 and 11.7% (8.4%–15.0%) in

2010, corresponding to 227 and 384 million of affected cases in 1990 and 2010, respectively. This estimate is an order of magnitude higher than the one presented in the 2001 World Health Report, estimating a world-wide prevalence of COPD of 10.1 per 1000 population (12.1 per 1000 men and 8.1 per 1000 women) [157]. A 2006 global review conducted by Halbert and colleagues reported a pooled prevalence of 9.2% (7.2-11.0), based on 26 spirometry-based estimates - a figure much closer to our estimates [21]. In the 2005 BOLD study, conducted in 12 sites globally and based on post-bronchodilator FEV₁/FVC<70%, the overall prevalence of Stage II or higher COPD was 10.1% (men 11.8% and women 8.5%) [40], which is again much closer to our results. Given that the estimates presented in the 2001 World Health Report were based on doctor's diagnosis and included all ages, this may explain the departure from spirometrybased estimates. All spirometry-based estimates to date seem to be comparable and may be indicative of the usefulness of spirometry as a gold standard for COPD diagnosis in population-based studies.

The highest COPD prevalence estimated in this study was observed in the American region, with an estimated prevalence of 13.3% and 15.2% in 1990 and 2010, respectively. Moreover, we estimated that 113 million COPD cases should be expected in Western Pacific region in 2010, almost doubling the estimated for 1990 which stood at 60 million. In the South East Asia, we estimated about 66.4 million COPD cases in 2010. Comparing our results to other estimates from previous studies, in the PLATINO multicentre study conducted across five South–American cities, which applied the same survey approach as the 2005 BOLD study, crude prevalence of COPD ranged from 7.8% in Mexico city to 19.7% in Montevideo [23]. A total of 12.2 million COPD cases, corresponding to an overall prevalence of 14.3%, was estimated for the urban population

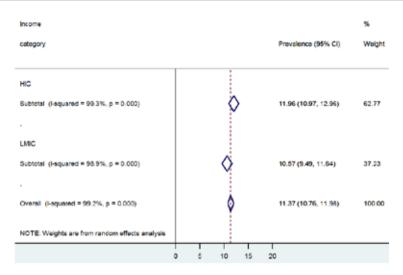


Figure 4. Overall pooled crude prevalence of COPD by World Bank income category.

 Table 4. Summary of overall COPD cases and prevalence rates in people aged 30 years or more (estimates derived from epidemiological model)

	19	90	20)10	% INCREASE IN COPD CASES
	Cases (millions)	Prevalence (%)	Cases (millions)	Prevalence (%)	
World	227.3	10.7 (7.3–14.0)	384.0	11.7 (8.4–15.0)	68.9
AFRO	14.1	9.8 (8.9–10.7)	28.5	11.4 (10.5–12.3)	102.1
AMRO	41.6	13.3 (12.9–13.7)	72.0	15.2 (14.9–15.5)	73.1
EMRO	13.4	11.8 (10.1–13.5)	29.3	13.4 (11.8–15.1)	118.7
EURO	54.2	11.8 (11.6–12.0)	66.4	13.7 (13.5–13.9)	22.5
SEARO	44.5	7.9 (7.5–8.4)	75.1	9.7 (9.3–10.1)	68.8
WPRO	59.5	9.2 (9.0–9.4)	112.7	11.1 (10.9–11.3)	89.4
Urban	120.9	13.2 (10.0–16.4)	230.3	13.6 (11.2–16.9)	90.5
Rural	106.3	8.8 (6.5–11.1)	153.7	9.7 (7.6–11.8)	44.6

COPD - chronic obstructive pulmonary disease

[23]. A mathematical model derived from prevalence of known COPD risk factors in 12 Asia-Pacific sites estimated about 57 million moderate-to-severe COPD cases in people aged 30 years or more in 2002, which is equivalent to a prevalence of 6.3% in the Asia Pacific region [158]. This figure is considerably larger than the WHO estimate for the region, which stood at 3.9% [157]. In addition, the regional working group reported that the number of COPD cases in China in 2002 should be expected to reach 38.2 million, with a prevalence of 6.5% [158]. This is again about 2.5 times higher than the estimates reported by the WHO [157]. Such differences in the regional pooled prevalence rates reported by separate authors may be linked to heterogeneities arising from differences in survey methodologies, population structure, subject's age and case identification [159]. Moreover, experts have reported that despite the apparently large burden of COPD in Western Pacific and South East Asia, there are few good epidemiological surveys on COPD in these regions [22]. For example, in a recent review in India, McKay and colleagues reported that they could not identify a single high quality study that provided detailed estimate of COPD prevalence using a relatively standard spirometry-based definition, and were therefore unable to perform a meta–analysis [160]. This was also observed in our study, as there were only three studies retained in India with only two of these providing age– and sex–specific COPD prevalence rates. However, we managed to include several large epidemiological surveys conducted in China, which actually had the highest number of retained studies (22 studies) of all the 52 countries represented (see Table s4 in **Online Supplementary Document**).

In the WHO EURO region, we noted the lowest increase in total number of COPD cases between 1990 and 2010 (22%). This may reflect the reduction in prevalence of smoking in Europe through intensive public health measures and legal regulations. According to the European Health Interview Survey (EHIS), the prevalence of COPD in 2008 among people aged at least 15 years in 16 EU member states ranged from 1.2% to 6.2%, with a mean

Table 5. Estimated number of COPD cases (in thousands) and prevalence by 5-year age groups and WHO regions (estimates derived from epidemiological model)	l number of	COPD case	s (in thousa	nds) and pre	valence by	5-year age β	groups and V	NHO region	s (estimates	derived from	ı epidemiolo	ogical model)		
Age (years)	AFRO		AMRO		EMRO		EURO		SEARO		WPRO		WORLD	
	1990	2010	1990	2010	1990	2010	1990	2010	1990	2010	1990	2010	1990	2010
30–34	2123.771	4795.619	5612.298	7809.886	2160.789	4817.729	5211.630	7524.854	8278.109	9429.498	6870.982	9683.379	30257.579	44060.964
35–39	2008.300	4243.869	5388.764	8020.309	1967.288	4325.147	5460.654	7595.221	7597.037	9656.235	7996.018	13297.535	30418.062	47138.315
40-44	1851.101	3722.464	4940.857	8193.717	1715.856	3968.634	5359.191	7509.439	5987.177	9823.378	6927.851	14807.541	26782.034	48025.172
45-49	1711.139	3356.237	4278.075	8705.217	1527.214	3577.205	4750.212	7363.516	5349.059	9464.399	6122.079	13200.449	23737.780	45667.023
50-54	1553.436	3004.563	3880.853	8293.600	1417.907	3202.697	5962.870	7009.837	4943.444	8899.492	6235.365	12475.879	23993.876	42886.069
55-59	1390.896	2651.316	3657.247	7479.966	1284.976	2675.335	5598.557	6476.111	4235.755	7858.034	6258.808	13161.340	22426.240	40302.102
60-64	1172.591	2219.778	3612.586	6401.209	1115.220	2094.671	5987.521	5532.130	3240.639	6080.409	5583.637	10297.357	20712.194	32625.554
65–69	923.106	1775.713	3293.108	5088.149	884.636	1658.040	5084.118	4231.163	2277.483	5002.799	4648.526	8015.963	17110.977	25771.827
70–74	658.987	1296.303	2640.100	4059.690	630.898	1301.601	3325.209	4808.956	1533.480	3971.306	3779.514	6852.798	12568.188	22290.654
75-79	397.162	827.323	2041.759	3221.004	402.706	911.945	3570.859	3588.680	739.897	2635.409	2642.263	5333.326	9794.645	16517.688
80+	281.660	615.016	2277.784	4770.635	307.511	760.336	3899.732	4727.433	304.694	2243.969	2403.848	5585.976	9475.228	18703.365
Total 30+	14072.150	14072.150 28508.201	41623.431	72043.382	13415.001	29293.340	54210.554	66367.341	44486.775	75064.929	59468.891	112711.542	227276.802	383988.734
% Prevalence 30+	9.79	11.39	13.31	15.19	11.82	13.43	11.83	13.70	7.92	9.68	9.20	11.14	10.67	11.71
Lower 95% CI	8.92	10.52	12.97	14.85	10.14	11.75	11.63	13.50	7.49	9.25	9.01	10.95	7.34	8.38
Upper 95% CI	10.67	12.26	13.65	15.54	13.49	15.10	12.03	13.89	8.36	10.11	9.40	11.34	14.01	15.04

prevalence of 3.1% [161], but EHIS was based on patient's self-reported diagnosis of COPD. Experts have raised concerns that COPD is often under-diagnosed when based on self-reporting of COPD diagnosis, even in high-income settings, and that the true prevalence rates may be considerably higher [162].

Several authors have reported that the epidemiological evidence on COPD in African region is still very limited and that this has affected the response to its growing burden in the region [16,34,163,164]. We estimated a prevalence of about 11% in 2010, amounting to 29 million COPD cases in the region. This is similar to a recent continent-wide estimate of more than 26 million cases in 2010 [34]. Epidemiological data are also very limited in the Middle East and North Africa [165]. Based on scarce available evidence, it appears that the EMR had the lowest absolute number of COPD cases in 1990 among the world regions, with 13 million (prevalence of 12%). However, the region then recorded the highest percentage increase by the year 2010 of 119%. Smoking rates in the Middle East and in many Mediterranean countries have reportedly been high [165]. This may imply that the burden of COPD in EMRO region could have been considerably under-estimated in the year 1990.

Several studies reported that urbanization is an important risk in the development of COPD [9,39]. We estimated over 230 million cases of COPD among global urban dwellers in 2010, accounting for almost 60% of all COPD cases. The rapid rate of urbanization in many parts of the world, especially in LMIC, may contribute to an increasing prevalence of COPD globally [39]. Moreover, the prevalence of COPD among men was consistently higher than in women across all world regions, settings and income categories. Some authors question the independent etiological role of gender in the development of COPD [166], given that the risk profile among men favours the development of disease. Recent reviews suggested that increased tobacco use among women in high-income countries and the higher risk of exposure to indoor air pollution (such as biomass fuels used for cooking and heating) in low- and middle income countries may contribute to reducing gender differences in COPD in future [1].

Our study has a number of limitations. Although we identified a considerable number of studies for this review, they were not proportionately distributed across the WHO regions, nor were the sample sizes from the regions proportional to regional populations. More than 46% of the data points were from the European region, meaning that the overall results may over-represent the burden of COPD in Europe. On the other hand, African region (4%), South East Asian region (4%) and Eastern Mediterranean region (5%) are all grossly under-represented, highlighting the lack of good quality prevalence data outside of the highincome countries.

Another important limitation relates to the differences in case definitions and diagnostic guidelines employed across

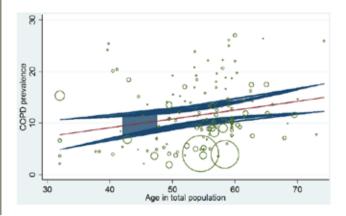


Figure 5. Epidemiological model based on meta–regression: The model is based on extracted crude COPD prevalence rates and adjusted for the study period and mean age of subjects from each study (the size of each bubble corresponds to the sample size from the respective study).

studies over time. In our analysis, we required spirometry as the standard diagnostic parameter, given the concerns raised over alternative definitions of COPD. Across all retained studies, the definition based on FEV/FVC<70% was used in the large majority of studies, but this still does not address all possible sources of variation in case definition. Some authors even question the use of a fixed FEV,/FVC ratio mainly because it has no statistical basis and because choosing 0.7 as a cut, off point – instead of 0.68 or 0.72, for example - is essentially arbitrary [29]. Experts have argued that this fixed criterion may potentially over-diagnose COPD in the elderly, as lung elasticity decreases with age, which reduces FEV, more than FVC [30]. Hence, using a fixed ratio can result in under-diagnoses in younger patients, and more frequent diagnoses in the elderly. The use of a lower limit of normal (LLN) has been suggested instead, and this is described as the lower fifth percentile of a reference population [31]. It is calculated by subtracting the standard deviation (multiplied by 1.64) from the mean [31]. However, some studies suggest that LLN may miss subjects with COPD [32]. This variation in COPD diagnosis is especially pertinent in LMICs, where undiagnosed or poorly treated asthma, bronchiectasis, tuberculosis or some other obstructive airway disease may be more prevalent and possibly misdiagnosed as COPD [17]. Even when the FEV/FVC<70% criterion was consistently applied, some studies were based on pre-bronchodilator values, rather than post-bronchodilator values, as recommended by

GOLD. In addition, it was often not fully explained how exactly was spirometry performed and what was the protocol. A number of technical issues could have affected the estimates, such as the choice of spirometer, the level of training of the operator, and the process of collection and storage of spirometry measurements. Finally, physicians' knowledge of guidelines can also pose a barrier to spirometry use in settings where it is available [167].

An additional limitation is associated with the choice of our epidemiological model, which was mainly based on age of the examinees. There are several other important predictors that could have been incorporated into the model if the information was available from the retained studies, including those related to study sites, income levels, smoking, socio–economic determinants of health, occupational exposures and others. However, the studies that we retained would rarely report these important covariates, so we could not use them in our model.

Meanwhile, it is worth noting that most of the studies (83%) included in this review were published after the year 2000, and encouragingly, the number of epidemiological studies focusing on COPD has been steadily increasing over the past two decades. This upward trend provides an indication of an increased awareness and recognition of COPD as a growing global health burden, and the need to strengthen research base and improve and standardize the methods.

Our findings suggest a high and growing prevalence of COPD, both globally and regionally, with substantial variation in trends between different world regions. The estimates presented here are consistent with other spirometrybased reviews on the burden of COPD. As with any other public health problem, increased political commitment and funding remains crucial, particularly in LMIC settings. Governments and policymakers must consider strengthening regulations to address occupational and environmental risk factors, regulate tobacco use and improve public awareness. A combined use of patient- and physician targeted educational interventions could also help [168]. The efforts of BOLD, aiming to standardize methodology and definitions, must be supported, and other research entities should strongly consider adopting similar methods or collaborating with BOLD in order to provide epidemiological results that are more comparable in and among populations. It is only through such concerted effort that the current high global COPD burden may be reduced in the coming decades.

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Authorship declaration: IR and KYC conceptualized the study. SC, CL and CB conducted the literature review for all databases. DA and AP performed all statistical analyses. DA, IR and KYC drafted the paper, with help from SC, CL and CB. Then, ET, HN, DG, DS, HC and AS provided useful additional input into the first draft. They also contributed to writing of the final version of the paper and checked the paper for important intellectual content.

Declaration of interest. IR and HC are co-editors-in-chief of the Journal of Global Health. To ensure that any possible conflict of interest relevant to the journal has been addressed, this article was reviewed according to best practice guidelines of international editorial organizations. Authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). None of the participating authors has a conflicting financial or other interest related to the work detailed in this manuscript.

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Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: Systematic review and meta–analysis

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Correspondence to: Dr Harish Nair Centre for Global Health Research Usher Institute of Population Health Sciences and Informatics University of Edinburgh Old Medical School Teviot Place Edinburgh EH8 9AG United Kingdom harish.nair@ed.ac.uk **Background** Respiratory syncytial virus (RSV) is the most common pathogen identified in young children with acute lower respiratory infection (ALRI) as well as an important cause of hospital admission. The high incidence of RSV infection and its potential severe outcome make it important to identify and prioritise children who are at higher risk of developing RSV–associated ALRI. We aimed to identify risk factors for RSV–associated ALRI in young children.

Methods We carried out a systematic literature review across 4 databases and obtained unpublished studies from RSV Global Epidemiology Network (RSV GEN) collaborators. Quality of all eligible studies was assessed according to modified GRADE criteria. We conducted meta–analyses to estimate odds ratios with 95% confidence intervals (CI) for individual risk factors.

Results We identified 20 studies (3 were unpublished data) with "good quality" that investigated 18 risk factors for RSV–associated ALRI in children younger than five years old. Among them, 8 risk factors were significantly associated with RSV–associated ALRI. The meta–estimates of their odds ratio (ORs) with corresponding 95% confidence intervals (CI) are prematurity 1.96 (95% CI 1.44–2.67), low birth weight 1.91 (95% CI 1.45–2.53), being male 1.23 (95% CI 1.13–1.33), having siblings 1.60 (95% CI 1.32–1.95), maternal smoking 1.36 (95% CI 1.24–1.50), history of atopy 1.47 (95% CI 1.16–1.87), no breastfeeding 2.24 (95% CI 1.56–3.20) and crowding 1.94 (95% CI 1.29–2.93). Although there were insufficient studies available to generate a meta–estimate for HIV, all articles (irrespective of quality scores) reported significant associations between HIV and RSV–associated ALRI.

Conclusions This study presents a comprehensive report of the strength of association between various socio–demographic risk factors and RSV–associated ALRI in young children. Some of these amenable risk factors are similar to those that have been identified for (all cause) ALRI and thus, in addition to the future impact of novel RSV vaccines, national action against ALRI risk factors as part of national control programmes can be expected to reduce burden of disease from RSV. Further research which identifies, accesses and analyses additional unpublished RSV data sets could further improve the precision of these estimates.

(i)

Globally, respiratory syncytial virus (RSV) is the most common pathogen identified in young children with ALRI, as well as an important cause of hospital admissions [5]. It is estimated that in 2005 there were about 33.8 million new episodes of ALRI which were RSV positive in children younger than 5 years and about 10% of these were severe enough to warrant hospitalisation. It is also estimated that RSV attributable mortality in children younger than 5 years was around 53255 in–hospital deaths and up to 199260 overall deaths globally in 2005, with 99% of these occurring in developing countries.

RSV is known to be more likely to have a severe outcome in children with certain pre–existing chronic medical conditions, resulting in higher rate of hospitalisation and higher risk of death. A case-control study in southwest Alaska indicated that underlying medical conditions, such as prematurity, chronic lung disease and heart disease, were associated with an increased risk of RSV hospitalisation [6]. Another systematic review reported that the case fatality ratio among children hospitalised with RSV infection was higher in children with chronic lung disease, congenital heart disease or prematurity, compared to otherwise healthy children [7]. The high incidence of RSV infection, as well as its potentially severe outcome, makes it important to identify and prioritise children at high risk of developing RSV–associated ALRI. To date, there has been only one systematic review published over a decade ago that assessed the strength of association between various risk factors and RSV–associated ALRI [8]. There have been no recent comprehensive systematic reviews that included the recent literatures reporting the association of various putative risk factors and RSV–associated ALRI in young children. Therefore, we conducted a systematic review to identify studies investigating the association between potential risk factors and RSV–associated ALRI in children younger than five years. We aimed to assess the quality of available evidence and present summary meta–estimates of the strength of association between multiple risk factors and RSV–associated ALRI to identify targeted prevention strategies.

METHODS

Search strategy and selection criteria

We conducted a systematic review according to the PRIS-MA guidelines. The search was conducted across the following electronic databases: Medline, Embase, Global Health and LILACS. The search terms used are detailed in Appendix S1 in **Online Supplementary Document**. We further hand searched the reference lists of relevant papers for eligible articles. All searches were limited to between January 1995 and July 2015, and there were no publication status or language restrictions applied. Eligible studies were observational studies or randomized controlled trials that assessed the relationship between RSV–associated ALRI and risk factors of interest. **Table 1** provides the selection criteria in detail.

Two investigators (TS and EB) conducted independent literature searches and extracted data using standardised data extraction template. Any discordance or uncertainties regarding relevance or inclusion were arbitrated by HN.

Table 1. Eligibility criteria for selection of studies in the systematic review

nclusion criteria:	
Published from January 1995 to July 2015	
Providing data for children younger than 5 y	
Focusing on children with a diagnosis of ALRI and laboratory confirmed RSV illness	
Reporting association between socio-demographic risk factors and RSV-associated ALRI	
Sample size ≥50 children below 5 y	
Study design–observational studies (case–control or cohort) or randomized controlled trials (placebo arm only)	
Reporting results on risk factors based on univariable or multivariable analysis	
Exclusion criteria:	
Definitions used for ALRI or risk factors, not clearly stated or inconsistently applied	
Focusing on risk factors solely among high–risk study population (eg, preterm babies, children with congenital heart disease, Thronic lung disease and immunosuppression etc.)	
neligible control group (eg, RSV negative ALRI cases, children hospitalised for acute infections)	
Methods for analysis not clearly reported	

Data from unpublished studies provided by RSV Global Epidemiology Network (RSV GEN) collaborators were reviewed (by TS) for quality and inconsistencies. RSV GEN is a working group established to collect unpublished data in order to evaluate the disease burden of RSV worldwide.

The protocol of this review was published in PROSPERO database (No. CRD42015017923).

Definitions

We used RSV-associated ALRI as the outcome of interest, which includes clinical pneumonia and bronchiolitis. This was to recognize these common manifestations in young children with viral ALRI [9], and the limitations of the WHO case definition to reliably differentiate bronchiolitis from pneumonia [1]. ALRI was defined as cough or dyspnoea with age-related tachypnoea, while severe ALRI was defined as cough or dyspnoea with lower chest wall indrawing or an acute respiratory infection severe enough to warrant hospital admission. The control group was defined as children without RSV infection (children without respiratory symptoms) or healthy (children without any symptoms). Countries were categorised as developing or industrialised according to the "Levels and trends in child mortality-report 2014" by UNICEF [10]. The Alaskan native population in America was considered to share some epidemiological features with populations in developing countries with similar socioeconomic and demographic risk factors for respiratory infections in both populations [11].

We recognized that the definitions for some risk factors used in the included studies varied substantially (Appendix S2 in **Online Supplementary Document**). Where there were several slightly different definitions (which may result in differing strengths of association between risk factor and outcome), we pooled the studies into one meta–analysis (where possible) and then conducted a sensitivity analysis. The definitions of risk factors included in the following meta–analysis were listed in **Table 2**.

Quality assessment

The quality of each study was assessed by using a modified GRADE scoring system [12] focusing on the following aspects: study design, quality of control group, sample size, analysis method, bias, confounding factors and geographical spread of studies (Appendix S3 in **Online Supplementary Document**). We calculated the overall score for each study after assessing each criterion as listed above. Studies with cumulative score ≤ lower quartile (25th percentile) of all scores were considered to have "low quality" and they were excluded in the final estimate. Also a sensitivity analysis was run to show whether the results differ when we included these "low–quality" studies.

Statistical analysis

In included articles or unpublished studies, data about risk summary measure (odds ratio and relative risk) with 95% CI for risk factors of interest were extracted as provided (univariable and multivariable analysis). If such summary data were not reported, we calculated the same (where feasible) using data reported in the paper.

Using STATA (Stata Statistical Software version 11.2, StataCorp LP, College Station TX, USA) we conducted a meta–analysis of risk factor specific odds ratios and reported pooled estimates with corresponding 95% CIs

Table 2. List of the various definitions of risk factors for RSV-associated ALRI included in meta-analysis

RISK FACTOR	Definition					
Prematurity:	Gestational age <37 weeks					
	Gestational age <33 weeks					
Low birth weight	Birth weight <2.5 kg					
Gender	Male					
Siblings	Mention of siblings or other children living in the household					
Maternal smoking	Maternal smoking during pregnancy					
History of atopy	Positive family history of asthma or atopy					
Low parental education:	No parent having bachelor's degree					
	Education of primary caregiver: 1–7 y or no schooling					
	<12 y maternal education					
	<11 y maternal education					
Passive smoking	Smokers in the household					
Daycare center attendance	Attendance at daycare center					
Indoor air pollution	Use of biomass fuels for cooking or a description of indoor smoke					
No breastfeeding	No breastfeeding					
Crowding	>7 persons in household					
Multiple births	Twins or triplets					
HIV	Confirmed presence of HIV infection in child					

ALRI – acute lower respiratory infection, RSV – respiratory syncytial virus, HIV – human immunodeficiency virus, y – years

RESULTS

We identified 2694 articles through literature search, of which only 23 studies [6,14-35] fulfilled our strict eligibility criteria. After including an additional 4 studies (Rasmussen, unpublished; Rath, unpublished; Singleton, unpublished; Zar, unpublished) provided by RSV GEN collaborators, 27 studies in total were included in the analysis (Figure 1). Six studies provided data on risk factors for RSV-associated ALRI [19,22,27] (Rasmussen, unpublished; Rath, unpublished; Zar, unpublished) and 21 studies provided data for RSV-associated hospitalised ALRI. Fourteen studies were from industrialised countries and 13 studies were from developing countries. A map of locations of these 27 study sites is given in Appendix S5 in Online Supplementary Document. Table 3 shows more characteristics of these 27 included studies. According to the modified GRADE scoring system, the scores of included studies varied from 2.5 to 11 with 25th percentile score of 6.25 (Appendix S4 in Online Supplementary Document). There were 7 studies which had scores ≤6.25 [20,22,31,32,34,35]

(Rath, unpublished). **Table 4** presents the final results for risk factors with meta–estimate ORs after excluding "low– quality" studies (20 studies). Forest plots for these risk factors are shown in Appendix S6 in **Online Supplementary Document**. Those "low–quality" studies were also included in a sensitivity analysis (Appendix S7 in **Online Supplementary Document**).

Prematurity (gestational age <37 weeks)

Prematurity has been defined variously in the included studies. One of the studies [29] used gestational age <38 weeks as definition for prematurity, three studies [14,20,26] used gestational age <36 weeks and nine studies used gestational age <37 weeks. Only studies using definition of gestational age <37 weeks were included in meta-analysis. Among these nine studies, two [16] (Singleton unpublished) reported the associations using multivariable analysis and the others used univariable analysis. Two studies (Singleton, unpublished; Zar, unpublished) were based on settings categorised as developing countries, while the rest were from industrialised countries. One study (Zar, unpublished) was community-based, another (Rath, unpublished) included outpatients and inpatients and the other 7 studies were hospital-based. Two studies [31] (Rath, unpublished) were considered to be "low-quality" studies. After excluding these two studies, the odds ratio meta-estimate was 1.96 (95% CI 1.44-2.67). Alternatively metaestimate was 1.47 (95% CI 0.98-2.21) if all studies irrespective of quality scores were included.

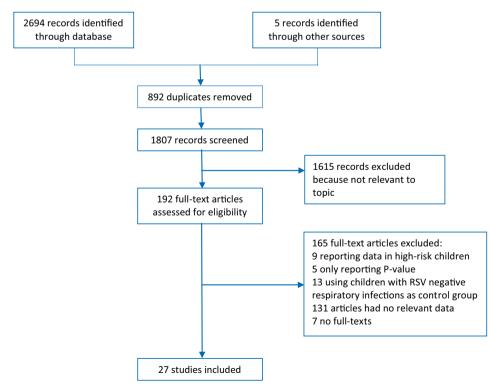


Figure 1. Flow diagram for the selection of studies.

Study	Study period	Study design	Age	Case ascer- tainment	Case definition	Sample size	RSV DETECTION	Risk factors included
Hvidovre, Denmark [29]	May 2004–May 2005	Prospective birth cohort	<1y	IP	ARI	217	NPS; PCR	PR, BF, S, PS, MS
Denmark[28]	1997–2003	Case-control	<18m	IP	ARI	15380	RSV database	M, HOA, DCA, S, MS
Utrecht, Netherlands [19]	Jan 2006–Dec 2008	Prospective birth cohort	<1y	IP, OP	ALRI	298	Nasal/throat swab; PCR	BF, M, HOA, PE, DCA, MS
Colorado, USA [15]	1998–2002	Cross-sectional	<4y	IP	P, B	4847	ICD–9 RSV codes	Altitude
San Marcos, Guatemala [27]	Oct 2002–Dec 2004	Randomized controlled trial	<18m	IP, OP	ARI	NA	NA; IF	IAP
Kilifi, Kenya [22]	May 2003–Apr 2007	Birth cohort	<4y	С	ALRI	469	NPW; DFA	MB, PE, MA, C, S, PS
Soweto, South Africa [20]	Mar 1998–Dec 2004	Prospective cohort	<6y	IP	ALRI	39836	NPA; IF	PR, HIV
South–western Netherlands [25]	Oct 1996–Apr 1999	Retrospective cohort	<2y	IP	ARI	NA	NPA; DFA/ culture	PR, LBW, M
9 perinatal networks, France [17]	Mar 2008 to Apr 2009	Retrospective & prospective cohort	<1y	IP	В	498	NPA; IF	PR
Kiel, Germany [31]	Jul 1996–Jun 1999	Cross-sectional	<2y	IP	ARI	NA	NPA; PCR	PR
Bohol, Philippines [23]	Jul 2000–Dec 2004	Retrospective cohort	<5y	IP	ALRI	10913	NA; PCR/ culture	M, PE, MA, S
Townsville, Australia [24]	Jan 1997–Jun 2004	Case-control	<3y	IP	ALRI	750	NPA; DFA	PR, LBW, M, S
Tennessee, USA [14]	Jul 1989–Jun 1993	Retrospective cohort	<1y	IP	ARI	3553	NA	PR, M, PE, S, MS
2 Danish counties, Denmark [21]	1990–1994	Case-control	<2y	IP	ALRI	7632	NPA; DFA	PR, LBW, S, MS
Basque Country, Spain [16]	Jul 1996–Jun 2000	Case-control	<2y	IP	ALRI	14343	NPA; IF	PR, LBW, MB, M,
Wellington Hospital, New Zealand [18]	June/July–October, 2003–2005	Case-control	<2y	IP	В	11411	NPA; DFA	PR, MB, M, MS
Alaska, USA [6]	Oct 1993–Sep 1996	Case-control	<3y	IP	ALRI	542	NPA; IF	BF, PE, C, S, S
3 hospitals in western region, Gambia [30]	1993–1995	Case-control	<5y	IP	ALRI	641	NPA; IF	HOA, M, C, S, PS, M, LPW, IAP
Italy [26]	Oct–Apr, 2000–2004	Case-control	≤4y	IP	ALRI	437	Nasal sample; IF	PR, LBW, BF, M, HOA, PI, S, PS
Alaska, USA (Singleton, unpublished)	Oct 2006–Sep 2007	Case-control	<3y	IP	ALRI	68	NPS; PCR	PR, BF, C, IAP, PS
Oshikhandass, Pakistan (Rasmussen, unpublished)	Apr 2012–Mar 2014	Case-control	<5y	С	ALRI	93	NPS; PCR	C, M, PE, S, IAP, PS
Soweto, South Africa [32]	Mar 1997–Mar 1998	Cross-sectional	2–23m	IP	ALRI	24000	NPA; DFA	HIV
3 sites, South Africa [33]	Jan 2010–Dec 2011	Cross-sectional	<5y	IP	ALRI	835060	NPA; PCR	HIV
Alaska, USA [34]	1995–2012	Cross-sectional	<ly< td=""><td>IP</td><td>ALRI</td><td>NA</td><td>NPA; DFA/ culture</td><td>C, IAP, LPW</td></ly<>	IP	ALRI	NA	NPA; DFA/ culture	C, IAP, LPW
Alaska, USA [35]	2000–2004	Cross-sectional	<1y	IP	ALRI	NA	NPA; DFA/ culture	LPW
Paarl, South Africa (Zar, unpublished)	Mar 2012–Dec 2014	Prospective cohort	<3y	С	ALRI	159	NPS; RT–PCR	PR, LBW, BF, M, HOA, PE, S, PS, MS, DCA, MA, C, IAP, PI
Berlin, Germany (Rath, unpublished)	Apr 2010–Mar 2014	Prospective cohort	<5y	IP, OP	ALRI	666	NPS/NPA; RT–PCR	PR, LBW, M, C

Table 3. Characteristics of 27 included studies

Case ascertainment: IP – inpatient, OP – outpatient; C – community. Case definition: ALRI –acute lower respiratory infection, ARI – acute respiratory infection, P – pneumonia, B – bronchiolitis. RSV detection: NPA – nasopharyngeal aspirate, NPS – nasopharyngeal swab, NPW – nasopharyngeal wash, PCR – polymerase chain reaction, IF – immunofluorescence, DFA – direct fluorescent antibody test, IFA – indirect fluorescent antibody test. Risk factors included: P – prematurity, LBW – low birth weight, BF – no/lack of exclusive breastfeeding, MB – multiple births, M – male, HOA – history of atopy, PE – low parental education, S – siblings, PS – passive smoking, MS – maternal smoking, DCA – daycare center attendance, MA – malnutrition, C – crowding, IAP – indoor air pollution, PI – previous illness, HIV – human immunodeficiency virus, LPW – lack of plumbed water, NA – not available, y – year, m – month

Prematurity (gestational age <33 weeks)

This risk factor was considered as a subgroup (more severe) of children with gestational age <37 weeks. Three hospital–based studies [14,21,25] from industrialised countries reported significant associations between prematurity (gestational age <33 weeks) and RSV–associated ALRI using multivariable analysis. The overall odds ratio meta–estimate was 2.68 (95% CI 2.02–3.55). Five additional studies [14,21,25] (Rath unpublished; Zar, unpublished), two of which were from developing countries [20] (Zar, unpublished), reported odds ratios using univariable analysis. The PAPERS

Table 4. Meta–estimate of odds ratio for risk factors excluding studies with quality score ≤6.25 (ie, "low–quality")

Risk factor	Multivariable <i>a</i>	NALYSIS	Multivariable and univariable analysis		
	No. of studies	Meta–estimate OR (95% confidence interval)	No. of studies	Meta–estimate OR (95% confidence interval)	
Prematurity (gestational age <37 weeks)	2	_	7	1.96 (1.44–2.67)	
Low birth weight	2	_	5	1.91 (1.45–2.53)	
Being male	6	1.32 (1.24–1.40)	12	1.23 (1.13–1.33)	
Siblings	6	1.53 (1.20–1.95)	11	1.60 (1.32–1.95)	
Maternal smoking	4	1.34 (1.26–1.42)	7	1.36 (1.24–1.50)	
History of atopy	1	_	5	1.47 (1.16–1.87)	
Low parental education	4	1.23 (0.73–2.09)	6	1.40 (0.94–2.08)	
Passive smoking	4	1.40 (0.65–3.00)	8	1.29 (0.96–1.73)	
Daycare center attendance	2	_	3	1.61 (0.98–2.64)	
Indoor air pollution	4	0.69 (0.35–1.37)	5	0.81 (0.42–1.57)	
No breastfeeding	1	_	3	2.24 (1.56–3.20)	
Crowding (>7 persons in household)	1	_	3	1.94 (1.29–2.93)	

OR – odds ratio

inclusion of these studies resulted in the odds ratio meta– estimate of 2.74 (95% CI 1.59–4.71). Two studies [20] (Rath, unpublished) were considered to be "low quality". After excluding them, the final odds ratio meta–estimate was 2.79 (95% CI 2.19–3.55).

Low birth weight

The six included studies used birth weight <2.5 kg to define low birth weight. One study [21] from Denmark used a definition of <3.0 kg, thus it was not included in the meta–analysis. Two hospital–based studies [16,25] [16,25] from industrialised countries reported significant associations between low birth weight and RSV–associated ALRI using multivariable analysis. Four additional studies [24,26] (Rath, unpublished; Zar, unpublished), one of which (Zar, unpublished) was from a developing country, reported odds ratios using univariable analysis. When data from these studies were combined with the data from studies using multivariable analysis, the overall odds ratio meta–estimate was 1.37 (95% CI 0.85–2.21). After excluding one study with "low quality" (Rath, unpublished), the final meta–estimate was 1.91 (95% CI 1.45–2.53).

Being male

Five hospital-based studies [14,18,23,25,28] and one community-based study (Rasmussen, unpublished), reported associations between being male and RSV-associated ALRI using multivariable analysis. Only two of them reported non-significant associations [18] (Rasmussen, unpublished). The overall odds ratio meta-estimate was 1.32 (95% CI 1.24–1.40). Seven additional studies [16,19,24,26,30] (Rath, unpublished; Zar, unpublished), two of which were from developing countries, reported the odds ratios using univariable analysis. Two studies [19] (Rath, unpublished) were based on hospital inpatients and outpatients and another one (Zar, unpublished) was based on active community ascertainment. The inclusion of these studies did not alter the odds ratio meta–estimate substantially (OR 1.21, 95% CI 1.12–1.32). Excluding one "low–quality" study (Rath, unpublished), the final meta–estimate was 1.23 (95% CI 1.13–1.33).

Siblings

Six hospital-based studies [14,21,23,24,28,29], one of which was from a developing country [23], reported associations between siblings (mention of siblings or other children living in the house) and RSV-associated ALRI using multivariable analysis. Only one of them reported a non-significant association [21]. The overall odds ratio meta-estimate was 1.53 (95% CI 1.20-1.95). Six additional studies [6,22,26,30] (Rasmussen, unpublished; Zar, unpublished), one of which was from an industrialised country [26], reported odds ratios for siblings and RSV-associated ALRI using univariable analysis. Three studies [22] (Rasmussen, unpublished; Zar, unpublished) were based on active community ascertainment and reported risk estimates for RSV-associated ALRI. The inclusion of these studies did not have any substantial effect on the odds ratio meta-estimate (OR 1.62, 95% CI 1.34-1.95). One study [22] was denoted as "low quality". The final meta-estimate was 1.60 (95% CI 1.32–1.95) after excluding this study.

Maternal smoking

Four hospital–based studies [14,18,21,28], all of which were from industrialised countries, reported associations between maternal smoking during pregnancy and hospitalised RSV–associated ALRI using multivariable analysis. Only one of them reported a non–significant association [18]. The overall odds ratio meta–estimate was 1.34 (95% CI 1.26–1.42). Three additional studies [19,29] (Zar, unpublished) reported data using univariable analysis. Two community–based studies from the Netherlands and South Africa [19] (Zar, unpublished) reported non–significant odds ratios for maternal smoking and RSV–associated ALRI and another hospital–based study from Denmark [29] reported a significant odds ratio. The inclusion of these studies resulted in a similar odds ratio meta–estimate of 1.36 (95% CI 1.24–1.50). All studies were considered to be of "good quality".

History of atopy

One hospital–based study [28] from Denmark reported a significant association between history of atopy (positive family history of asthma or atopy) and hospitalised RSV–associated ALRI using multivariable analysis. Four additional studies [19,26,30] (Zar, unpublished), two of which were from developing countries [30] (Zar, unpublished), reported the odds ratios using univariable analysis. One study [19] was based on both inpatient and outpatient settings in hospital and another one (Zar, unpublished) was community–based study. The overall odds ratio meta–estimate was 1.47 (95% CI 1.16–1.87). No studies had "low quality".

Low parental education

Definitions of low parental education varied among the included studies. Four studies [14,19,23] (Rasmussen, unpublished), two of which were from developing countries [23] (Rasmussen, unpublished), reported associations between low parental education (no parent having bachelor's degree, <11 or <12 years maternal education, primary or no schooling) and RSV-associated ALRI using multivariable analysis; two of them reported significant associations. One study [19] was based on both inpatient and outpatient settings in hospital. One study (Rasmussen, unpublished) was a community-based study. The overall odds ratio meta-estimate was 1.23 (95% CI 0.73-2.09). Three additional studies [6,22] from developing countries reported odds ratios for low parental education (≤12 grade or primary or no schooling) and RSV-associated ALRI using univariable analysis. Two studies [22] were based on active community ascertainment and reported RSV-associated ALRI. The inclusion of these three studies resulted in a slightly higher odds ratio meta-estimate of 1.77 (95% CI 0.91-3.46). After excluding one low-quality study [22], the meta-estimate was 1.40 (95% CI 0.94-2.08) in the end.

Passive smoking

Three hospital–based studies and one community–based study reported the associations between passive smoking (smokers in the house) and RSV–associated ALRI using multivariable analysis with the meta–estimate 1.40 (95% CI 0.65–3.00) [29,30] (Rasmussen, unpublished; Singleton, unpublished). Only one study from Denmark [29] reported a significant association. Five additional studies [6,22,24,26]

(Zar, unpublished), two of which were from industrialised countries [24,26], reported odds ratios for passive smoking and RSV–associated ALRI using univariable analysis. Only two studies reported significant associations [6,24]. Two studies [22] (Zar, unpublished) were based on active community ascertainment. After combining studies using multivariable analysis and univariable analysis, the odds ratio meta–estimate was 1.23 (95% CI 0.95–1.60). One study [22] was "low quality". After excluding this study, the final meta–estimate was 1.29 (95% CI 0.96–1.73).

Daycare center attendance

One hospital–based study [28] from Denmark reported a significant association between daycare center attendance and hospitalised RSV–associated ALRI using multivariable analysis (OR 1.40, 95% CI 1.15–1.70). One study [19] from the Netherlands based on both inpatient and outpatient settings in hospital reported a non–significant association between daycare center attendance and RSV–associated ALRI using multivariable analysis (OR 5.80, 95% CI 0.76–44.4). One community–based study (Zar, unpublished) from South Africa also reported a non–significant association using univariable analysis. Overall, the odds ratio meta–estimate was 1.61 (95% CI 0.98–2.64). All studies were of "good quality" and were included in the final analysis.

Indoor air pollution

Three hospital–based studies [30,34] (Singleton, unpublished) from Alaska and Gambia reported associations between indoor air pollution (woodstove in household) and hospitalised RSV–associated ALRI using multivariable or univariable analysis. Another study [27] from Guatemala based on both inpatient and outpatient settings in hospital reported a non–significant association using multivariable analysis (OR 0.76, 95% CI 0.42–1.16). A further two studies (Rasmussen, unpublished; Zar, unpublished) based on active community ascertainment from Pakistan and South Africa also reported non–significant associations using univariable analysis. Overall, the meta–estimate of odds ratio was 0.86 (95% CI 0.57–1.31). One study [34] was considered as having "low quality", thus after excluding this study, the final meta–estimate was 0.81 (95% CI 0.42–1.57).

No breastfeeding

Three hospital-based studies [6] (Singleton, unpublished; Zar, unpublished) from developing countries reported as sociations between no breastfeeding and RSV-associated ALRI. Only one of them [6] reported a significant association based on univariable analysis. These three studies all had "good quality" and the overall meta-estimate of odds ratio was 2.24 (95% CI 1.56–3.20). Another four studies [19,26,29] (Zar, unpublished), three from industrialised countries, reported odds ratios for lack of breastfeeding (no breastfeeding for first 14 days, <3 months breastfeeding or lack of exclusive breastfeeding) and RSV–associated ALRI. Only one study [29] reported a significant odds ratio based on multivariable analysis. One study [19] was based on both inpatient and outpatient settings in hospital and another one (Zar, unpublished) was community–based. Since these four studies used substantially different definitions for breastfeeding, meta–analysis was not carried out.

Crowding

Included studies used varied definitions for crowding. Four studies [6] (Rath, unpublished; Singleton, unpublished; Zar, unpublished) reported associations between crowding (>7 persons in household) and RSV-associated ALRI. One study (Rath, unpublished) from Germany only had 5 children with crowding (5 in case group and 0 in control group). The prevalence of crowding is too small to generate a reliable estimate, thus this study was not included in analysis. One of them (Singleton, unpublished) reported the association using multivariate analysis. One study (Zar, unpublished) was community-based and the other two were hospitalbased. These three studies all had "good quality". Overall, the meta-estimate of the odds ratios was 1.94 (95% CI 1.29-2.93). Other studies used substantially different case definitions and, for these, meta-analysis was not done. Two studies [6,34] from Alaska presented significant associations between crowding (defined as ≥ 2 persons/room in household and an increase of 20% of households >1.5 persons/ room) and hospitalised RSV-associated ALRI. One hospital-based study [30] from Gambia also reported a significant association using the definition of ≥ 10 people living in the household. Two community-based studies from Kenya [22] and Pakistan (Rasmussen, unpublished) reported nonsignificant associations with definitions of \geq 3 siblings/room or >7 persons/room.

Multiple births

Only one study [18] from New Zealand reported a nonsignificant association between multiple births (twins or triplets) and hospitalised RSV–associated ALRI using multivariable analysis. Two additional studies reported nonsignificant odds ratios using univariable analysis. One study from Spain [16] presented the association for multiple births and hospitalised RSV–associated ALRI while another study from Kenya [22] was based on active community–based case ascertainment. After combining these three studies, the odds ratio meta–estimate was 1.41 (95% CI 0.98–2.03). However, one study [22] was considered as "low–quality" and thus no meta–estimate was available after excluding this study.

HIV

Three hospital–based studies [20,32,33] from South Africa reported significant associations between HIV (confirmed presence of HIV infection in child) and RSV–associated ALRI. One of them reported an age–adjusted association and provided data for two years separately [33]. The overall meta–estimate of odds ratio was 3.74 (95% CI 2.47– 5.66). Two of them [20,32] were considered to be of "low quality". Thus no meta–estimate was available after we excluded these two "low–quality" studies.

Malnutrition

Only three studies were included. Two community–based studies from Kenya [22] and South Africa (Zar, unpublished) reported non–significant associations between malnutrition (weight for age ≤2 standard deviations) and RSV–associated ALRI using univariable analysis (OR 1.28, 95% CI 0.75–2.21) and 1 (95% CI 0.4–2.9). Another hospital–based study [23] from the Philippines reported a significant association between measures less than or equal to median growth (weight for age) and hospitalised RSV–associated ALRI using multivariable analysis (OR 1.34, 95% CI 1.02–1.76).

Altitude

Only one hospital-based study [15] from Colorado reported a significant association between high altitude and hospitalised RSV-associated ALRI using multivariable analysis, stratified by age and control group. The odds ratio of RSVassociated hospitalised ALRI among infants at high altitude (>2500 m) compared to moderate altitude (1500–2500 m) was 1.30 while it was 1.22 when compared to low altitude (<1500 m). Also, the odds ratio among children aged 1–4 years old in high altitude was 1.80 when compared to moderate altitude and 1.62 when compared to low altitude.

Previous illness

One hospital–based study [26] from Italy reported a significant association between no previous RSV infections and hospitalised RSV–associated ALRI using univariable analysis (OR 1.85, 95% CI 1.02–3.36). Another community–based study from South Africa (Zar, unpublished) reported a significant association between previous history of ALRI and RSV–associated ALRI using univariable analysis (OR 3.9, 95% CI 1.2–12.5).

Lack of plumbed water (available within the household)

Two hospital-based studies [34,35] from Alaska reported significant associations between lack of plumbed water or low proportion in-home water service (<80%) and hospitalised RSV-associated ALRI (OR 1.45, 95% CI 1.19–1.78

and OR 2.81, 95% CI 2.42–3.26 respectively). However, both studies were considered to be of "low–quality". Another study from Gambia [30] reported "tap in compound" compared to other water sources and the adjusted OR was 1.75 (95% CI 0.85–3.60). This number was converted to be comparable to those two studies mentioned above.

DISCUSSION

Our study presents the most up-to-date and comprehensive report of the strength of association between various socio-demographic risk factors and RSV-associated ALRI in children younger than five years old. After excluding "low-quality" studies, we identified a total of 18 putative risk factors, of which 8 (prematurity, low birth weight, being male, siblings, maternal smoking, history of atopy, no breastfeeding and crowding ≥7 persons in household) were observed to be significantly associated with RSV-associated ALRI. Ten additional risk factors (low parental education, passive smoking, daycare center attendance, indoor air pollution, HIV, multiple births, malnutrition, higher altitude, previous illness and lack of plumbed water in the household) were also observed to have an association with RSV-associated ALRI in 1-3 studies. However, for some of these risk factors (eg, lack of breastfeeding, crowding), meta-analysis could not be performed to generate odds ratio meta-estimate as case definitions were substantially different or sufficient studies were not available (eg, HIV, multiple births). Therefore, the associations between these risk factors and RSV-ALRI require further study.

There was considerable variation among the 27 included studies (including "low-quality" studies). Nine [14,17,19,20,22,23,25,29] (and Rath, unpublished) were cohort studies; 11 [6,16,18,21,24,26,28,30] (and Rasmussen, unpublished; Singleton, unpublished; Zar, unpublished) were case-control studies; 6 [15,31-35] were crosssectional studies; and 1 [27] was a randomized controlled trial. Most studies used questionnaires or interviews (of caretakers or parents) to gather information on various risk factors, which could be a source of several biases, such as response bias, recall bias, interviewer bias and misclassification bias. Other potential biases also existed. For example, there could be follow-up bias in cohort studies. Among eleven case-control studies, only 7 [6,21,24,28,30] (Rasmussen, unpublished; Zar, unpublished) selected a control group matched by date of birth and/or sex and/or location of residence, which could introduce substantial bias in the selection of controls in studies which did not use matched control groups.

There were substantial differences with regards to the number of confounders adjusted in each study. Seven studies [15,18,23,25,27,28] (and Singleton, unpublished) used multivariable analysis to adjust for all other risk factors of interest investigated in the same study. Some also adjusted for age at third dose of pneumococcal conjugate vaccine, age at risk and weight for age *z*–score at first vaccination [23], or population distribution of education level, households that were living below poverty level and race [15]. One study reported age adjusted relative risk [33]. Four studies [20,29,32,33] also reported concurrent bacteraemia or coinfection with other viruses. Another 7 studies used univariable analysis, and 12 studies reported estimates using both multivariable and univariable analysis.

The quality score of each study obtained from modified GRADE scoring system varied from 2.5 to 11 with a mean of 7.6. There were 7 studies with "low quality" (quality score \leq 6.25). Most of them were not designed as case-control studies, did not consider biases within the research, did not take into account of potential confounders or reported estimates using multivariable analysis. A sensitivity analysis was carried out to include these "low-quality" studies. The meta-estimate OR from sensitivity analysis did not differ substantially from the analysis where only studies with quality scores >6.25 were included (Appendix S8 in the Online Supplementary Document). However, this quality assessment tool did not address all aspects related to study quality since we only looked into seven of these: study design, quality of control group, sample size, analysis method, bias, confounding factors and geographical spread of studies. More detailed and appropriate quality assessment tools should be applied and studies with higher quality would be needed to generate more reliable results.

It is noteworthy that there was substantial heterogeneity in the specific definition for a risk factor in each of the included studies, which limited our analysis. For example, six studies used a definition of birthweight <2.5 kg to define low birth weight, while one study [21] used a higher threshold-birthweight <3.0 kg, and was therefore excluded from the meta-analysis. Nine studies defined prematurity as gestational age <37 weeks, while three studies [14,20,26] used gestational age <36 weeks and another one [29] used <38 weeks. After excluding "low-quality" studies and these four studies using different definitions of prematurity, the meta-estimate of the association between prematurity (gestational age <37 weeks) and RSV-associated ALRI was 1.96 (95% CI 1.44-2.67), which was similar to the alternative estimate 1.98 (95% CI 1.56-2.52) when all studies irrespective of quality scores were included. Only one study (Zar, unpublished) reported that prematurity was determined using ultrasonography. Seven studies defined low parental education using five different definitions-no parent having bachelor's degree [19], 1-7 years of education or no schooling for primary caretaker [22] (Zar, unpublished), 1-5 years of education or no schooling

for parents (Rasmussen, unpublished), <12 years maternal education [6,14] and <10 years maternal education [23]. Since there were insufficient studies in each category, we did not conduct a subgroup meta-analysis. Similarly crowding was defined using substantially different definitions in the included studies: >7 persons living in household [6] (Singleton, unpublished; Zar, unpublished), ≥ 10 persons in household [30], ≥2 persons per room [6] (Zar, unpublished), ≥ 3 siblings less than 6 years old sleeping in the same room [22], >7 persons sleeping per room (Rasmussen, unpublished), an increase of 20% in number of households >1.5 persons/room [34]. Therefore, once again, we did not conduct a subgroup meta-analysis in this instance except for the definition of >7 persons living in household. The substantial variability in reporting definitions for the same risk factor require that standardised definitions should be proposed for future studies, which will improve the comparability of these studies.

Furthermore, there was variation in the age groups of participants included in each study. Only six studies included children younger than five years old [20,23,30,33] (Rath, unpublished), and 21 studies included children in narrower age bands (eg, 0–11months, 0–18 months, 0–23 months). Thirteen studies focused on children younger than two years old, among which, six studies included only infants (0–11 months) [14,17,19,29,34,35]. Since data from different age groups were pooled together, and RSV is predominantly an infection in children aged below 2 years [5], we may have overestimated the association between various risk factors and RSV–associated ALRI in children aged 0–59 months.

Also, the sample size of each study varied considerably. We only included studies with sample size greater than 50, as specified in our eligibility criteria. However, among the 27 included studies, the sample size varied from 68 (Singleton, unpublished) to 835 060 [33]. This is reflected in the wide confidence intervals of the ORs for some studies with small sample size, indicating less precise estimates.

Another limitation is that we did not have access to individual patient data on risk factors for RSV–associated ALRI. Further research should focus on obtaining individual patient data from previous studies or ongoing studies, such as multi–center Pneumonia Etiology Research for Child Health (PERCH) project. With these patient level data, we could have a better understanding about the role of each risk factor in RSV–associated ALRI (particularly with regard to prematurity) and adjust for possible confounders in a pooled analysis.

The definitions of some risk factors were similar or the same as those reported in a review [36] investigating risk factors for severe ALRI (for which etiology was not further specified), which indicates that pneumonia and RSV–associated ALRI do share a few socio–demographic risk factors which are amenable to interventions, such as maternal smoking, passive smoking and no breastfeeding. Appendix S9 in the **Online Supplementary Document** shows the comparison of strength of association of risk factors identified in both reviews. The strength of association between risk factors and severe ALRI was generally slightly stronger than the corresponding ones in RSV–associated ALRI. Several risk factors were only investigated for severe ALRI, such as incomplete immunization, vitamin D deficiency, anemia, zinc deficiency, birth interval, birth order, and vitamin A deficiency, while some risk factors were only explored for RSV–associated ALRI (siblings, history of atopy, multiple births, high altitude, lack of plumbed water in the household).

Compared to the previous review [8] conducted over one decade ago, this review presented an overview of a larger number and more recent studies investigating more risk factors associated with RSV and summarized the findings using meta-analysis. Both reviews shared similar results for some risk factors, such as being male, crowding/siblings and day care attendance. Also, we provided more evidence for some risk factors which had an unclear role with regard to RSV (passive smoking, low parental education). Additionally, we identified more risk factors associated with RSV which were not available in previous review due to insufficient evidence (prematurity, low birth weight, maternal smoking, history of atopy, indoor air pollution, no breastfeeding). However, race/ethnicity, age of acquisition of RSV as well as birth during the first half of RSV season, which were investigated in previous review, were not evaluated in this review because no recent relevant studies were found. Moreover, several risk factors which were reported in some studies were not included in this search strategy or in the analysis, such as, siblings' death, parents' nationality, parents' occupation, their roles also remained unknown [30].

Further research on this topic should identify, seek access to and analyze additional unpublished RSV data sets to further improve the precision of these estimates. This should include, where possible, investigation of possible association with risk factors which have been reported to show association with (all cause) ALRI: incomplete immunization, vitamin D deficiency, anemia, zinc deficiency, birth interval, birth order, and vitamin A deficiency.

CONCLUSION

RSV is a major cause of hospital admission and mortality among young children, especially in developing countries [5]. Our study assessed the role of putative socio–demographic risk factors for RSV–associated ALRI. Many of these risk factors are similar to those that have been identified for (all cause) ALRI and thus, in addition to the potential future impact of novel RSV vaccines currently under development and evaluation, national action against ALRI risk factors as part of national control programmes [37] can be expected to reduce burden of disease from RSV. The evidence generated from this study could be used to model the global, regional and national estimates of RSV–associated ALRI. Since some risk factors are preventable, policy makers and public health practitioners could develop targeted interventions to decrease the prevalence of these risk factors in order to reduce RSV–associated ALRI disease burden. However, this evidence base is limited by paucity of data. Therefore, large scale, high quality multivariable studies should be conducted on a priority basis to better understand the role of each individual risk factor for RSV–associated ALRI in diverse settings

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Burden of respiratory syncytial virus infections in China: Systematic review and meta–analysis

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Dr Moe H Kyaw Sanofi Pasteur 1 Discovery Avenue Swiftwater, PA 18371 USA moe.kyaw@sanofipasteur.com **Background:** Respiratory syncytial virus (RSV) is the most important cause of acute respiratory tract infection (ARTI) related morbidity and mortality worldwide. However, the disease burden due to RSV has not been systematically summarized in China.

Method: A systematic search was performed in the Chinese BioMedical Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang database and PubMed to identify available published RSV studies in China.

Results: A total of 489641 patients with ARTIs from 135 studies were included in the analysis. Among patients with ARTIs, RSV accounted for 18.7% (95% confidence interval CI 17.1–20.5%). The prevalence of RSV was highest in infants (26.5%, 95% CI 23.7–29.5%) and lowest in those aged ≥16 years (2.8%, 95% CI 1.3–6.1). A higher prevalence of RSV was seen in inpatients (22%, 95% CI 19.9–24.2%) than in outpatients (14%, 95% CI 9.6–19.9%). RSV type A accounted for 63.1% (95% CI 52.3–72.8%) of all RSV infections. RSV infections occurred mainly in winter and spring. The most common clinical manifestations were cough, production of sputum, wheezing and fever.

Conclusion:RSV is the leading cause of viral ARTIs in China, particularly in infants and young children. Our findings are valuable for guiding the selection of appropriate therapies for ARTIs and implementation of preventive measures against RSV infections. Our data further supports the development of a successful RSV vaccine as a high priority.

Acute respiratory tract infections (ARTIs) are an important cause of morbidity and mortality among children under the age of 5 years [1,2], with the highest number of deaths occurring in developing countries [3]. In China, pneumonia is the leading cause of deaths in children under 5 years old with an estimated >30 000 deaths annually [4]. Viruses have been considered as the most frequent causes of ARTIs. The predominant viruses associated with ARTIs in children include respiratory syncytial virus (RSV), influenza virus (IV), parainfluenza virus (PIV), human rhinovirus (HRV) and adenovirus (ADV) [5,6].

RSV is the leading cause of ARTIs in early childhood. It is estimated that 33.8 million new episodes of RSV-associated acute lower respiratory infection

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(ALRI) occurred worldwide in children younger than 5 years, with at least 3.4 million episodes representing severe RSV– associated ALRI necessitating hospital admission [7]. The pattern of RSV infections is variable and related to season, socio–demographic and characteristics of study populations.

China has the largest child population and has substantial differences in climate from region to region. It has a variety of temperature and rainfall zones, including continental monsoon areas. The total population of children aged 14 years or younger is estimated to be 230 million. Although the epidemiology of RSV infections has been studied in cities such as Beijing, Chongqing and Lanzhou [8–10], few RSV studies in China have been published in English. Therefore, we performed a systematic review and meta–analysis of published studies to evaluate the epidemiology of RSV infections in patients with ARTIS.

A better understanding of the epidemiology of RSV infections plays a key role for the prevention, control and treatment of ARTIs. The objective of this systematic review and meta–analysis was to evaluate the etiology, serotypes, clinical features, age distribution and seasonality associated with RSV infections in China.

METHODS

Search strategy

A systematic search was performed in indexed databases, including Chinese BioMedical Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang database and PubMed to identify available RSV studies in China. The following search terms were used: RSV or syncytial virus. Taking into account the quality of studies, high quality publications from the Chinese core journals (2014 edition) [11] were considered in the final analysis. The Library of Perking University evaluates all Chinese journals every four years and excludes lower quality journals using the quality measurement similar to the impact factors. To obtain recent data, the search strategy was limited to publications dated from January 2010 to Mar 2015. Details of the search strategy are presented in Appendix S1 in **Online Supplementary Document.**

Inclusion and exclusion criteria

To be included, the following criteria had to be fulfilled: 1) studies in humans; 2) studies in patients with ARTIs; 3) studies that had at least one following outcome: etiology of acute respiratory infections; seasonality; gender; age group; serotypes; clinical features; 4) studies published in Chinese or English.

Publications were excluded if they were: 1) animal experiments or basic research (examples, studies focus on principles or mechanisms using cells and tissues); 2) case reports, systematic review or meta–analysis; 3) replicates (when the same population was studied in more than one publication, only the latest one or the one with the most complete data was considered for the meta–analysis).

ARTIs was defined as patients who were present of one or more respiratory symptoms, including watery eyes, rhinorrhea, nasal congestion or sinus congestion, otitis media, pharyngitis, cough, sore throat, sneezing, headache, and muscle pain. Meanwhile, patients had at least one symptom during acute infection, with high fever (body temperature ≥38°C) or chillness or normal/low leukocyte count or who were diagnosed with pneumonia by chest radiography previously. Chest radiography was conducted according to the clinical situation of the patient, and pneumonia was defined as an acute illness with radiographic pulmonary shadowing (at least segmental or in one lobe) by chest radiography.

Literature screening and data extraction

Literature reviewers were divided into two parallel groups. Using the set criteria of inclusion and exclusion, the reviewers independently screened the literature by title, keyword and abstract. Any disagreement was solved by a third reviewer. If they were not sure whether the study should be included, the decision was made based on further review of the full texts. NoteExpress 2 (Aegean Software Corporation, Shanghai, China) was used for the bibliography management.

Two parallel groups independently extracted the following data from eligible studies: general information, methodological quality and outcome data. Inconsistencies between two groups were checked after data extraction. Any disagreements were solved by the third reviewer.

Quality assessment

This meta–analysis included various types of studies with different outcomes. Therefore, no pre–existing scale is directly suitable for the assessment. The 5–item specific rating scale was developed to assess the quality of studies. These included 1) Did the study report patients' information? 2) Did the study report diagnosis criteria of acute respiratory infection? 3) Did the study report specimen collection methods? 4) Did the study report statistical methods? Each item was scored on three scales; 0 indicating low quality, 1 indicating medium quality, and 2 indicating high quality. The score for each item was then added to give a composite score for the study, with a highest total score of 10. If the total score was equal to or greater than 8, we regarded the study as "good" quality.

Statistical analysis

The MetaAnalyst (Beta 3.13; Tufts Evidence–based Practice Center, Boston, USA) was used to conduct meta–analyses for pooled proportions and odds ratios. Considering heterogeneity across all studies, we chose a random–effects model to carry out meta–analysis using Der–Simonian Laird method. The publication bias was determined via Stata 12.0 (StataCorp LP, Texas, USA) using an Egger's test. Meta–analysis for combining the results of studies was weighted to provide the balanced results of all included studies.

RESULTS

Selection of studies

Of the total of 4852 studies identified through the databases, 135 studies were included in the analysis (**Figure 1**). Of the 135 studies, 123 studies were in children less than 16 years old and the remaining studies were in both children and adults. Of the 135 studies, 19 studies were published in English. The detailed information about author, publication year, province, age, specimen type, detection methodology, number of specimen and study outcomes are listed in Appendix S2 in **Online Supplementary Document**.

For the 135 studies, the quality evaluation score ranged from 5 to 10 points, with a mean \pm standard deviation of 7.7 \pm 1.3. There were 80 studies with a score of \geq 8. The summary of quality assessment is listed in Appendix S3 in **Online Supplementary Document**.

Etiology

The overall positivity rate of RSV among patients with AR-TIs was 18.7% (95% CI 17.1–20.5%), followed by HRV, human bocavirus (HBoV), IV, PIV, human metapneumovirus (HMPV), enterovirus, ADV and human coronavirus (HCoV). (**Table 1**).

	Table 1. Etiology	of acute	respiratory	[,] infection	in all a	ages
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Virus	No. articles included	Virus—positive	Total patients	Positive rate (%, 95% CI)
RSV	132	81747	489641	18.7 (17.1–20.5)
Rhinovirus	36	3647	31605	11.5 (9.8–13.5)
HBoV	45	5899	110345	6.8 (5.5–8.5)
IV	95	17115	262089	6.5 (5.4–7.7)
PIV	97	17515	264538	6.4 (5.6–7.2)
HMPV	59	5935	130620	4.3 (3.6–5.1)
Enterovirus	16	923	17689	4.0 (2.8–5.6)
Adenovirus	96	9618	275380	3.4 (2.9–3.9)
HCoV	39	1544	66048	2.6 (2.0–3.4)

RSV – respiratory syncytial virus, PIV – parainfluenza virus, IV – influenza virus, HMPV – human metapneumovirus, HBoV – human bocavirus; HCoV, Human coronavirus, CI – confidence interval

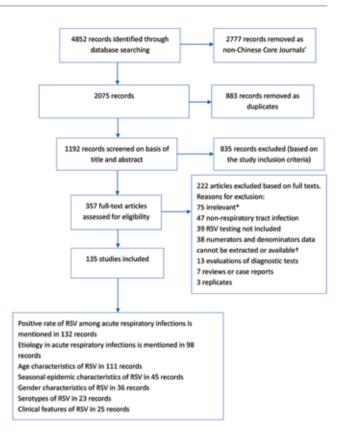


Figure 1. Flow diagram of literature search and selection. *Including: 1) Did not discuss respiratory tract infections or respiratory syncytial virus; or 2) only as background to discuss; or 3) used the abbreviation "RSV", but not referring to respiratory syncytial virus. †These studies reported/ included charts or risk ratios and the numerators and denominators were not available.

The prevalence of RSV was stratified into inpatients, outpatients, inpatients/outpatients and unknown category. RSV was found most frequently among inpatients 22.0% (95% CI 19.9–24.2%), followed by inpatients/outpatients, outpatients and unknown (**Table 2**).

Seasonal characteristics

A total of 45 studies reported the seasonality of RSV infections. Of these 45 studies, 28 studies reported monthly isolation rates and the remaining 17 studies reported quarterly. The peak of RSV infections mainly occurred in winter and spring (**Table 3**).

Gender characteristics

A total of 36 studies reported gender characteristics of RSV infections. Among 96 694 male patients, RSV was positive in 17 163 patients (20.4%, 95% CI 16.6–24.8%). Among 54 958 female patients, RSV was positive in 8364 (19.9%, 95% CI 16.0–24.4%).

 Table 2. Positive rate of RSV infection in acute respiratory tract infected patients

intected patients				
	No. articles included	Virus— positive	Total patients	Positive rate (%, 95% CI)
Settings:				
Inpatient	86	67319	366386	22.0 (19.9–24.2)
Outpatient	9	1061	9229	14.0 (9.6–19.9)
Inpatient/outpatient	45	8779	67826	15.8 (12.1–20.2)
Unspecified	95	4568	46200	11.4 (7.4–17.1)
Total	132	81747	489641	18.7 (17.1–20.5)
Age groups:				
0–6m	45	12522	43222	29.9 (26.2–33.8)
0–1y	65	29607	113386	26.5 (23.7–29.5)
0–3y	55	27544	130152	23.7 (20.9–26.9)
0-бу	47	17854	121717	19.5 (16.0–19.6)
0–16y	72	57193	351426	17.7 (5.5–8.5)
≥16y	7	440	18781	2.8 (1.3-6.1)
Inpatients only by age groups:				
0–6m	31	10690	35 592	32.4 (27.7–37.4)
0-1y	44	25259	97542	34.4 (28.9–40.4)
0–3y	37	20789	99951	24.3 (20.6–28.3)
0–бу	28	12446	88248	19.8 (16.4–23.7)
0–16y	45	46128	270359	20.0 (17.9–22.3)
≥16y	3	174	8604	2.8 (0.8–9.8)
Regions:				
Northeast	2	285	3003	9.5 (8.5–10.6)
North China	18	2203	26710	10.9 (6.3–18.4)
South China	23	10625	96413	15.7 (13.2–18.6)
East China	44	50001	273312	17.6 (15.3–20.2)
Central China	14	2978	16346	22.5 (16.8–29.5)
Northwest	9	1523	5010	27.6 (21.3–34.9)
Southwest	20	10375	35970	28.7 (25.7–32.0)
Multi–regions	2	3757	32877	14.7 (6.6–29.6)
Detection methodology†				
IF	51	41201	230033	17.0 (14.4–20.0)
PCR	73	32814	201063	19.9 (17.9–22.1)
Others	8	7732	58545	20.1 (15.8–25.3)

Table 3. Seasonal epidemic characteristics of RSV infection among acute respiratory infected patients

Month/ season*	No. articles included	RSV—positive	Total patients	Positive rate (%) (95% confidence interval)
Jan	17	1150	4672	24.7 (15.2–37.5)
Feb	17	1094	4311	25.1 (17.1–35.4)
Mar	17	849	4003	19.5 (13.5–27.4)
Apr	16	504	3174	17.4 (13.5–22.3)
May	15	181	2551	8.7 (6.1–12.3)
Jun	14	135	2945	5.5 (3.1–9.4)
Jul	14	105	2805	4.5 (36.8)
Aug	13	163	2605	7.0 (4.5–10.7)
Sep	14	183	2511	6.4 (3.6–11.3)
Oct	16	254	2935	7.5 (4.2–13.1)
Nov	17	597	3522	14.4 (8.8–22.5)
Dec	17	1049	3954	26.2 (17.9–36.8)
Spring	27	5627	37738	13.9 (11.1–17.4)
Summer	27	2008	31716	5.3 (3.7–7.6)
Autumn	27	4204	28223	11.8 (8.2–16.8)
Winter	27	9774	32937	22.7 (17.4–29.1)

*Spring – 1 March to 31 May, Summer – 1 June to 31 August, Autumn – 1 September to 30 November, Winter – 1 December to 28/29 February.

Table 4. Clinical characteristics of RSV related acute respiratory
infected patients

CLINICAL CHARACTERISTICS	No. of articles included	Symptomatic patients	RSV INFECTED PATIENTS	Percent (95% CI)
Cough	24	9880	11194	93.9 (91.0–96.0)
Expectoration	6	1578	2316	66.3 (43.8–83.2)
Wheeze	13	1768	2778	65.7 (56.5–73.8)
Fever	22	3738	10018	43.0 (37.5–48.7)
Rhinorrhea	8	1621	5669	42.7 (31.6–54.6)
Cyanosis	9	1346	4318	38.9 (15.8–68.2)
Tachypnea	11	2024	7737	32.2 (15.7–54.9)
Diarrhea	7	838	5272	18.8 (11.4–29.5)
Dyspnoea	8	1707	7918	12.8 (5.0–28.9)

†* PCR – polymerase chain reaction, IF – immunofluorescence, Others – refers to PCR/IF and RVP Fast, y – year, m – month, CI – confidence

RSV serotypes

There were 23 studies that reported RSV serotypes. Among 4172 RSV infected patients; type A, type B and mixed type A and B were detected in 2469 (63.1%, 95% CI 52.3–72.8%), 1611 (35.6%, 95% CI –6.0 to –46.6%) and 92 (1.2%, 95% CI 0.7–2.2%), respectively.

Clinical characteristics

Twenty–five studies reported the clinical manifestations of RSV infection. The most frequently reported clinical manifestations were cough, sputum production, wheezing and fever (**Table 4**).

Sensitivity analysis and publication bias

The conclusions remained robust and the outcomes did not alter significantly when only 'good' quality studies were evaluated in the sensitivity analysis. The overall RSV positivity rates were 19.7% (95% CI 17.7–21.9%) in all patients (n=79), 22.7% (95% CI 20.2–25.3%) in inpatients (n=53), and 13.8% (95% CI 8.3–22.0%) in outpatients (n=5).

Publication bias was tested using the Egger's test. No publication bias was detected when verifying the 132 publications that reported RSV positive rates in all patients (-0.27, 95% CI -1.19 to -0.65, P=0.563).

PAPERS

interval

DISCUSSION

RSV is the most common viral cause of ARTIs in developed and developing countries [7,12]. However, the available epidemiological data on RSV in China has not been systematically summarized in English. Our results highlight that RSV is the leading cause of viral ARTIs in China.

The burden of respiratory viral infections is difficult to measure and is likely to differ from country to country due to several factors such as socio–demographic distribution, seasonal variation, study design and diagnostic techniques. In our study, RSV was the most frequently detected pathogen among patients with ARTIs in all age groups studied. Consistent with other studies, RSV and HRV were the most prevalent viruses in children [2,13,14].

In the present study, only 12 studies reported the RSV infections in adult patients and the remaining 123 studies were in children. Infants aged ≤1 year were at higher risk of RSV associated ARTIs, compared with those in other age groups. This is consistent with the previous reports of RSV in both developed and developing countries [7,12,15,16]. The data show that RSV accounted for nearly 30% of all ARTIs in infants. Efforts to prevent RSV infections in infants can lead to a substantial reduction of RSV associated morbidity, mortality and medical costs in China. Further evidence of RSV disease burden can be established by adding RSV studies in existing influenza surveillance systems.

The relation between RSV infections and climate has been well documented [17,18]. In regions with persistently warm temperatures and high humidity, RSV activity is continuous throughout the year, peaking in summer and early autumn. In temperate climates, RSV activity is maximal during winter, correlating with lower temperatures. In areas where temperatures remain colder throughout the year, RSV activity also occurs almost continuously [17,18]. Most areas of China have a temperate climate. We found that the peak of RSV activity mainly occurred during winter and spring in China, which is similar to the previous reports [19–21]. This pattern of seasonality corresponds to the cold and dry seasons. However, we are unable to report regional differences in RSV activity due to limited data availability.

Based on genetic and antigenic variations in structural proteins, RSV isolates are subdivided into two major antigenic types (A and B). Both types are associated with mild to severe ARTIs [22–24]. Studies have shown that type A and B viruses co–circulate in the same area during epidemic periods and have various patterns of predominance [25–28]. However, the prevalence of each type may shift yearly and can vary among different communities [28–30]. Our analysis showed that type A was the predominant serotype accounting for 63.1% of all RSV infections. However, it is difficult to know how the sero–epidemiological trend changed in the recent years in China. This is because the study periods and locations varied substantially among included studies.

The studies we included differed in their methods of sampling and case–definition. Therefore, caution should be taken when interpreting the results. In our study, only 42 studies presented detailed criteria for case–definition. In addition, only 54 out of the 135 included studies used immunofluorescence for RSV detection. RSV was identified less frequently (17.0%) if only the results of studies based on immunofluorescent detection were included. In comparison with immunofluorescence, molecular diagnostics are more sensitive and specific [31,32]. In recent years, the introduction of nucleic acid based diagnostic tests has markedly improved our understanding of viral etiology among ARTI patients [33]. Therefore, the real burden of RSV in China is likely to be higher than our findings if more sensitive diagnostic methods are used.

These differences in case definitions and diagnostic techniques are likely to have impacted the results. Therefore, a random effects model was applied to take into account the heterogeneity between studies resulting in wider 95% CIs with more conservative estimates of the overall results [34]. In addition, the etiology data in the present study should be interpreted with caution. This is because restricting RSV to the title and abstract in the search criteria is a potential source of bias and might not be representative of all studies reporting other viruses. However, all included studies in current review tested for multiple viruses. Therefore, it is reasonable to assume that the use of correct denominator and numerators allow us to present the useful and informative etiology data available in these studies.

In conclusion, this systematic review and meta–analysis showed that RSV is the leading cause of ARTIs in China, particularly among infants. Our findings are valuable for guiding the selection of appropriate therapies for ARTIs and implementation of preventive measures against RSV infections. Despite the disease burden, no effective RSV vaccine is currently available. Our data further supports the development of a successful RSV vaccine as a high priority.



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Etiology of community acquired pneumonia among children in India: prospective, cohort study

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Joseph L. Mathew Additional Professor Advanced Pediatrics Centre PGIMER Chandigarh India 160012 dr.joseph.l.mathew@gmail.com **Background** Childhood community acquired pneumonia (CAP) is a significant problem in developing countries, and confirmation of microbial etiology is important for individual, as well as public health. However, there is paucity of data from a large cohort, examining multiple biological specimens for diverse pathogens (bacteria and viruses). The Community Acquired Pneumonia Etiology Study (CAPES) was designed to address this knowledge gap.

Methods We enrolled children with CAP (based on WHO IMCI criteria of tachypnea with cough or breathing difficulty) over 24 consecutive months, and recorded presenting symptoms, risk factors, clinical signs, and chest radiography. We performed blood and nasopharyngeal aspirate (NPA) bacterial cultures, and serology (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*). We also performed multiplex PCR for 25 bacterial/viral species in a subgroup representing 20% of the cohort. Children requiring endotracheal intubation underwent culture and PCR of bronchoalveolar lavage (BAL) specimens.

Findings We enrolled 2345 children. NPA and blood cultures yielded bacteria in only 322 (13.7%) and 49 (2.1%) children, respectively. In NPA, Streptococcus pneumoniae (79.1%) predominated, followed by Haemophilus influenzae (9.6%) and Staphylococcus aureus (6.8%). In blood, S. aureus (30.6%) dominated, followed by S. pneumoniae (20.4%) and Klebsiella pneumoniae (12.2%). M. pneumoniae and C. pneumoniae serology were positive in 4.3% and 1.1% respectively. Multiplex PCR in 428 NPA specimens identified organisms in 422 (98.6%); of these 352 (82.2%) had multiple organisms and only 70 (16.4%) had a single organism viz. S. pneumoniae: 35 (50%), Cytomegalovirus (CMV): 13 (18.6%), Respiratory Syncytial Virus (RSV): 9 (12.9%), other viruses: 6 (8.7%), S. aureus: 5 (7.1%), and H. influenzae: 2 (2.9%). BAL PCR (n=30) identified single pathogens in 10 (S. pneumoniae-3, CMV-3, S. aureus-2, H. influenzae-2) and multiple pathogens in 18 children. There were 108 (4.6%) deaths. The pattern of pathogens identified did not correlate with pneumonia severity or mortality.

Conclusions The majority of children with CAP have multiple pathogens (bacteria and viruses). *S. pneumoniae* and *S. aureus* predominate in NPA and blood respectively. CMV and RSV were the dominant respiratory viruses in NPA and BAL. The presence of multiple pathogens, especially organisms associated with nasopharyngeal carriage, precludes confirmation of a causal relationship in most cases.

Pneumonia is a leading cause of childhood morbidity and mortality globally. It is estimated that there were over 120 million episodes of pneumonia among children younger than five years during 2010-11; of which over 10% were severe episodes [1]. A recent systematic review estimated 0.22 pneumonia episodes per child-year in developing countries alone [2], with nearly one in eight cases progressing to severe disease. Yet another systematic review estimated nearly 12 million hospitalizations in 2010 due to severe pneumonia and 3 million due to very severe disease [3]. Pneumonia is also estimated to be responsible for almost 1 million deaths among children under 5 years old [4], with maximum burden in Africa and South Asia [3]. India has a high burden of childhood pneumonia and the disease accounts for about a guarter of the under-five mortality in the country [5]. Recognizing this burden, the World Health Organization (WHO) developed and disseminated a simple case definition for identification and treatment of pneumonia, which could be used by field-workers in resourcepoor settings [6-9]. It relies on the physiological principle that parenchymal lung disease results in compensatory tachypnea; therefore any tachypnea indirectly indicates parenchymal disease including pneumonia. This case definition is highly sensitive, and does not require chest radiography.

Traditional teaching attributes most cases of childhood community acquired pneumonia (CAP) to a few micro-organisms, mostly bacteria [8]. In recent decades, developed countries have witnessed a shift from bacterial to viral predominance on account of hygiene, sanitation, infection control, and vaccination policies. Recent systematic reviews of childhood pneumonia etiology suggest that in developing countries, a few bacteria (S. pneumoniae and H. influenzae) and viruses (Respiratory Syncytial Virus, Influenza virus) are associated with majority of childhood CAP [3,5,10-12]. A systematic review from India suggested that about 15-24% of bacterial pneumonia in South Asian countries can be attributed to S. pneumoniae [13]. Similarly data from the Invasive Bacterial Infection Surveillance (IBIS) network in India suggests that invasive Pneumococcal disease could be a significant public health problem in the country, contributing to significant morbidity and mortality [14]. However these data were not based on studies designed to determine pneumonia etiology.

The Pneumonia Research for Child Health (PERCH) project [15] is a 7–site case–control study to identify the cause of pneumonia among children in developing countries. However, none of the sites is located in India. Pilot data from PERCH reported 152 potentially pathogenic isolates among 108 hospitalized cases, using multiple microbiologic techniques on various body fluids. Viruses represented over 80% of the pathogens detected [16].

Conventional methods for determining etiology, such as bacterial culture of blood or nasopharyngeal swabs, and/or selective application of serological tests for a few organisms, are limited by poor sensitivity, or low specificity, or both. On the other hand, diagnostic techniques with greater specificity are limited by technical difficulty, invasive procedures, and high cost.

Accurate, reliable and rapid determination of etiology in childhood CAP is important because it would influence individual treatment decisions, antibiotic policy in the community, and also rational immunization policy at a national level. Currently, there is no study from India reporting etiology of CAP in a large cohort of children, using multiple biological samples, and various sensitive as well as specific microbiologic methods. We initiated the Community Acquired Pneumonia Etiology Study (CAPES) to address this knowledge gap by determining the microbiologic etiology of CAP in a cohort of Indian children using multiple biological specimens (blood, nasopharyngeal aspirates, bronchoalveolar lavage) and the relationship between etiology and pneumonia severity.

METHODS

This prospective study was carried out in the Union Territory of Chandigarh (located in north India with a population of 1.05 million residing in urban, rural and urban–slum areas, of whom 11.3% are children), over 24 consecutive months from 1 April 2011 to 31 March 2013. The study was coordinated from the Advanced Pediatrics Centre (APC) at PGIMER Chandigarh, a tertiary care centre with nearly 20000 annual in–patient admissions and 100000 out–patient visits.

Enrolment of children aged 1 month to 12 years, fulfilling the WHO IMCI case definition of CAP designed for children <5 years [6-8], was carried out through active and passive surveillance (Figure 1). Tachypnea was defined as respiratory rate >60/min for infants <2 months; >50/min for infants 2-12 months; >40/min for children >12-60 months; and >30/min for children >60-144 months. Active surveillance was conducted in 30 anganwadi clusters, selected to represent the population of Chandigarh, where trained research team members visited households daily, inquiring for clinical symptoms of pneumonia. Passive surveillance was carried out by research staff stationed in the Out Patient and Emergency Departments of the APC, by evaluating clinical signs of CAP in children presenting to these Departments. If symptoms were reported and tachypnea confirmed, the child was presented to a Medical Officer for confirmation and inclusion. Children with duration of illness >7 days; those who had received antibiotics for >24 hours at presentation or those with previous hospitalization within the preceding 30 days, were excluded. Children with wheeze received a single dose of bronchodilator (Salbutamol 0.15mg/ kg by nebulization), and those whose symptoms disappeared were excluded. All children received standard treatment including antibiotics, other medications as required and supportive care as per institution guidelines.

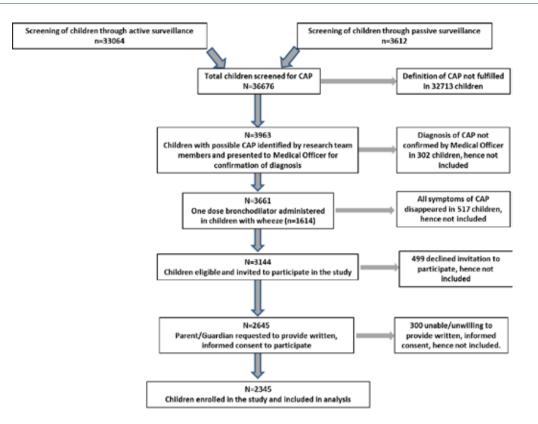


Figure 1. The screening process for children enrolled through passive or active surveillance. Trained research team members identified children with cough and /or difficult breathing, combined with tachypnea. If the child fulfilled WHO IMCI definition of CAP; confirmation of the diagnosis by a medical officer was required. Children whose symptoms of CAP disappeared with a single dose of bronchodilator were excluded. After obtaining written parental consent to participate, a total of 2345 children were enrolled in the study and included in analysis.

Clinical work-up

Each child underwent a detailed history for demographic data, presence of risk factors for pneumonia, and immunization status. After physical examination, pneumonia severity was categorized based on the WHO classification [6-8]. In addition, all children underwent chest radiography. The radiographs were subsequently independently read by two trained investigators and scored as per the WHO criteria [17]. Discordant results were resolved through mutual discussion. In addition, children who required endotracheal intubation were also offered fiber–optic bronchoscopy and bronchoalveolar lavage (BAL), based on clinical need.

Sampling and microbiological testing

A blood sample was drawn by venepuncture for routine investigations (hemogram, blood biochemistry). One to three ml blood was processed for bacterial culture using BACTEC 9240 (Becton Dickinson, Haryana, India) in Peds plus/F culture media (Becton Dickinson) [18]. The bottles were incubated at 37 °C for seven days and isolates were identified to species level by conventional biochemical and serological tests.

A nasopharyngeal aspirate (NPA) specimen was obtained from all children using a sterile, disposable suction catheter [19]. One aliquot was processed for bacterial culture and one aliquot was mixed with 3 ml saline and frozen at -80 °C for subsequent PCR analysis. BAL samples were similarly processed for bacterial culture and PCR. The Department of Medical Microbiology at PGIMER is accredited by the Government of India's National Accreditation Board for Testing and Calibration Laboratories (NABL).

Serum was stored at –80 °C for *M. pneumoniae* and *C. pneumoniae* IgM serology performed using commercially available kits (Calbiotech Inc USA) according to the manufacturer's instructions [20,21] and analyzed with an automated ELISA reader (SPECTROstar Nano, BMG LabTech, Germany) [22]. Serological tests were run in duplicate and only concordant results were labeled as positive or negative.

Multiplex PCR was performed on a subset of samples representing 20% of the cohort, selected through a randomization procedure stratifying by age, pneumonia severity and season. PCR was performed for detecting a panel of respiratory bacteria and viruses (Table S1 in **Online Supplementary Document**) at Xcyton Diagnostics Pvt Ltd, Bangalore, also NABL accredited, using the Syndrome Evaluation System (SES) for Pneumonia. The SES was standardized to attain 100% sensitivity and specificity using quantified virus panels available from Quality Control for Molecular Diagnostics (QCMD), UK [23]. (Table S2 in Online Supplementary Document). Limit of Detection for all DNA viruses was 250 virions/mL and 100 virions/mL for CMV and adenoviruses. For RNA viruses, QCMD proficiency panels of 2011 were used. Samples were thawed, centrifuged (3000 rpm×10 min) and re-suspended in 1 mL sample supernatant. Nucleic acids were extracted using commercially available Qiagen kits and cDNA was prepared using a commercial cDNA Archive Kit (ABI, USA) [24], both according to the manufacturer's instruction with the addition of pathogen specific primers. Amplification was carried out in Bio-Rad PTC200 thermal cycler and the detection of amplified products was facilitated using biotin labeled primers. Samples were categorized as negative or positive for any pathogen with internal controls (human housekeeping genes β 2-microglobulin and β -actin) included in each run as control for DNA and RNA extraction respectively.

Statistical analysis

Descriptive statistics of cohort characteristics and duration of various symptoms are presented with proportional distribution and median (IQR) respectively. Ordinal categorical data and mortality status was analyzed using test of linear association. Data analysis was conducted in IBM SPSS Statistics 22.0 [25].

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RESULTS

A total of 36676 children underwent active or passive surveillance for CAP. **Figure 1** shows the step–wise process used to enrol children. A total of 2345 children were enrolled and comprised the cohort included in the analysis.

Table 1 presents the baseline characteristics of children enrolled through active or passive surveillance. Children <12 months dominated in both groups. Severe and very severe disease was detected more frequently in children enrolled through passive surveillance. A total of 1145/2345 children (48.8%) were enrolled during the cold season from 16 November to 15 February; while the remaining (51.2%) were enrolled during the longer warm season. Acute malnutrition, defined as weight-for-age z score less than 3, was observed in 1008/2345 children (42.9%). Similarly, absent or deficient breastfeeding (defined as duration of breastfeeding <6 months for infants older than six months, or less than infant's age in those <6 months old) was more common in those enrolled through passive surveillance. These children were also more likely to be exposed to solid fuels as well as tobacco smoke in their homes. There were no major differences in gender, history of wheeze, previous history of Table 1. Baseline characteristics of children enrolled in the study*

	Active surveili	ANCE	Passiv survei	
	n= 746	%	n= 1599	%
Gender:				
Male	558	74.8	1123	70.2
Age group:				
1–2 months	10	1.3	142	8.9
3–12 months	295	39.5	887	55.5
13–60 months	382	51.2	424	26.5
61–144 months	59	7.9	146	9.1
Severity:				
Pneumonia	609	81.6	424	26.5
Severe pneumonia	131	17.6	870	54.4
Very severe pneumonia	6	0.8	305	19.1
Season:				
Cold	360	48.3	785	49.1
Warm	386	51.7	814	50.9
Malnutrition	249	33.4	759	47.5
Absent or deficient breast feeding	63	8.4	230	14.4
History of wheezing	112	15.0	200	12.5
History of >1 episodes of URI and/or diarrhea	207	27.7	415	26.0
Current or previous family history of TB	28	3.8	49	3.1
Past history of TB	11	1.5	25	1.6
Predominant use of solid fuel	223	29.9	764	47.8
Any use of solid fuel	257	34.5	816	51.0
Exposure to tobacco smoke at home	172	23.1	489	30.6

URI - Upper respiratory infections, TB - tuberculosis

*See Table S3 in Online Supplementary Document for definitions.

infections, or family history of tuberculosis in children enrolled through active or passive surveillance.

Table 2 presents symptoms reported by parents, clinical findings and radiography. Almost all children presented with cough, fever and fast breathing with median duration of symptoms being similar in those enrolled through active or passive surveillance. Parents reported wheezing during the current episode in approximately one-third of the children. Symptoms/signs suggesting greater severity of pneumonia were more frequently identified in those enrolled through passive surveillance. A larger proportion of these children also had WHO Class I and Class II chest X–rays.

There were 108 (4.6%) deaths; of these 107 occurred among those enrolled through passive surveillance (mortality rate 9.2%) and one among those enrolled through active surveillance (0.1%). Based on disease severity, the mortality rate was 1.2% for pneumonia, 4.7% for severe pneumonia and 15.8% for very severe pneumonia. A comparison between fatal and non–fatal cases suggested that age <12 months, oxygen saturation <95% and radiographic finding of consolidation (WHO Class I) were associated with mortality.

Table 3 summarizes the microbiology findings from cultureof different biological specimens. Blood culture results were

Table 2. Presenting symptoms,	clinical examination	findings and
chest radiography at enrolmer	nt into the study	

	Active sur	VEILLANCE	Passive sur	VEILLANCE
	n=746	%	n=1599	%
Symptoms at presentation:				
Fast breathing	698	93.6	1556	97.3
– median duration in days (IQR):	2 (1	L-3)	2 (1-	-3)
Cough	738	98.9	1459	91.2
– median duration (IQR):	4 (3	3–7)	4 (2-	-7)
Fever	545	73.1	1254	78.4
– median duration (IQR):	3 (2	2–5)	3 (2-	-5)
Difficult breathing	412	55.2	1351	84.5
– median duration (IQR):	2 (1	1–3)	2 (1-	-4)
Chest indrawing	156	20.9	1097	68.6
– median duration (IQR):	2 (1	L-3)	2 (1-	-3)
Wheezing	239	32.0	621	38.8
– median duration (IQR):	2 (2	2-3)	2 (1-	-3)
Altered mental status	60	8.0	395	24.7
Inability to drink	29	3.9	350	21.9
Clinical findings:				
Pallor	48	6.4	398	24.9
Cyanosis	6	0.8	101	6.3
Retractions	193	25.9	1178	73.7
Crackles	476	63.8	1225	76.6
Wheezing	289	38.7	553	34.6
Oxygen saturation:				
>95%	658	88.2	802	50.2
92–95%	65	8.7	402	25.1
<92%	23	3.1	393	24.6
Radiography findings:*				
WHO Class I	272	36.8	770	48.5
WHO Class II	179	24.2	482	30.4
WHO Class III	285	38.6	323	20.4
WHO Class IV	3	0.4	12	0.8
Mortality	1	0.1	107	9.2

IQR - interquartile range

*WHO categorization of chest radiography [17]: Class I=consolidation/ pleural effusion; Class II=interstitial pattern/infiltrate; Class III=no consolidation/infiltrate/effusion; Class IV=radiograph quality not sufficient for reading.

available in 2285 children (97.4%) and only 49 (2.1%) were positive for pathogenic species. NPA culture results were available in 2323 children (99.1%) and of these, potentially pathogenic organisms were identified in 322 (13.9%). BAL culture (performed in children requiring endotracheal intubation), 0–5 days (median 2 days) after enrolment was positive in only 3/30 children. In addition, serology was positive for *M. pneumoniae* in 103 (4.3%) and *C. pneumoniae* in 26 (1.1%).

Figure 2 summarizes the data from microbiologic analysis of respiratory specimens. Of the 469 NPA samples selected for multiplex PCR, only 428 (91%) could be fully processed and 422 samples (98.6%) yielded organisms (panel A in **Figure 2**). A single bacterium or a single virus was found in only 42 (9.8%) and 28 (6.5%) children respectively. *S. pneumoniae* dominated (n=35) followed by *S. aureus* (n=5) and *H. influ*-

Table 3. Bacterial culture in clinical specimens

Organism	BLOOD (N = 2285)	NPA (n = 2323)	BAL (n = 30)
S. aureus	15	22	1
S. pneumoniae	10	255	1
H. influenzae	4	31	_
K. pneumoniae	6	3	_
Acinetobacter spp*	5	1	1
S. typhi	3	-	_
Enterobacter spp	1	-	_
E coli	1	3	-
Pseudomonas spp	_	4	-
Stenotrophomonas maltophila	_	1	-
Yeast spp	_	1	_
Multiple	4†	1‡	_
Total	49	322	3

NPA-nasopharyngeal aspirate, BAL-broncho-alveolar lavage

*Acinetobacter Baumanii and Lwofii.

[†]Two children had *S. pneumoniae* + *S. aureus*; and one child each had *S. aureus* + *Enterococcus faecalis* and *Pseudomonas* + *E coli*

‡One child had Acinetobacter spp + K. pneumoniae

enzae (n=2). The single viruses identified were CMV (n=13) and RSV (n=9) followed by Rhinovirus (n=2), and one each of Influenza, Parainfluenza, Enterovirus and hMPV. *S. pneumoniae* was the dominant organism identified in NPA culture as well. A comparison of the bacterial yield from NPA by PCR and culture is shown in panel B in **Figure 2**.

Among the 428 children with NPA PCR results, 25 died and PCR showed diverse organisms distributed in a pattern similar to the 428 children (panel C in **Figure 2**). Among intubated children undergoing bronchoscopy as part of clinical care (n=30), only 2 samples were negative on PCR and the remainder showed organisms in a similar pattern to NPA PCR (panel D in **Figure 2**).

Since most NPA PCR samples yielded multiple pathogens, the data were analyzed with respect to etiology patterns rather than individual pathogens. These included combinations of two bacteria, two viruses, one bacterium plus one virus, or mixed i.e more than one bacteria and/or virus (panel E in **Figure 2**). The most common combination of pathogens in individual samples was *S. pneumoniae* and CMV (n=100) followed by 2 bacteria or 2 viruses.

In BAL samples, the single pathogens identified were *S. pneumoniae* (n=3), *S. aureus* (n=2), *H. influenzae* (n=2) and CMV (n=3); the majority of samples (n=18) showed multiple organisms (panel F in **Figure 2**) that were distributed in a pattern almost similar to NPA samples.

The complex microbial patterns on PCR were further analyzed with respect to disease severity (defined according to WHO criteria) but there were no apparent differences (**Figure 3**).

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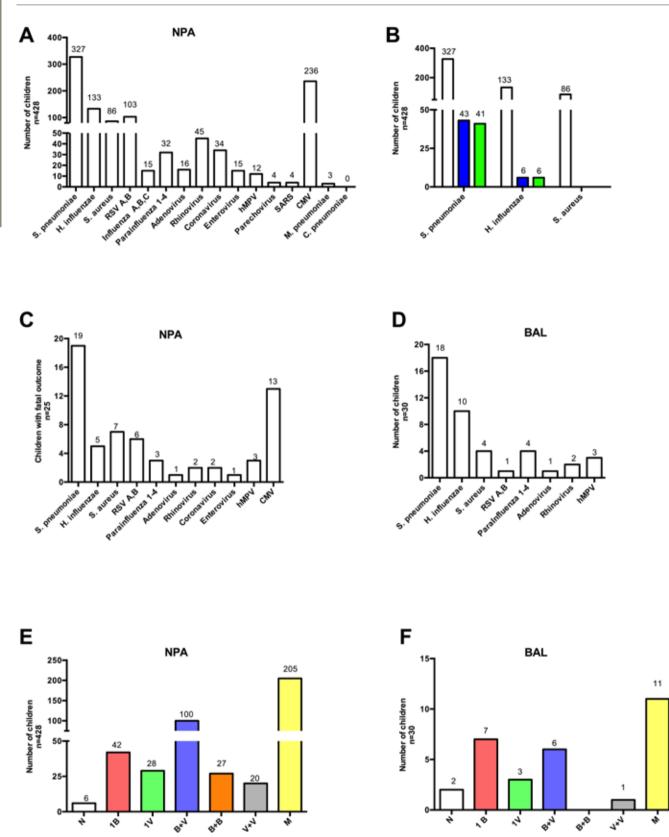


Figure 2. Microbiological findings in samples obtained from the sub–group (n=428) of children with CAP. The number above each bar represents the number of children with a positive result. (A) Nasopharyngeal aspirate (NPA) Multiplex–PCR findings (bacteria and viruses) in the sub–group (n=428). (B) Comparison of diagnostic yield of bacteria in NPA by PCR and culture indicates that PCR has a higher sensitivity; PCR (white bars), NPA (blue bars) and double positive samples (green bars). (C) NPA PCR findings in children with fatal outcome (n=25). (D) BAL PCR findings in children who were intubated and underwent broncho–alveolar lavage (n=30). Combinations of pathogens in (E) NPA samples (n=428) and (F) BAL samples (n=30). N–Nil, B–Bacteria, V–Virus, M–multiple organisms.

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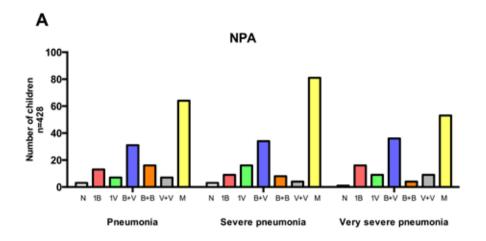


Figure 3. NPA Multiplex–PCR findings stratified by pneumonia severity as defined by WHO IMCI criteria in the sub cohort (n=428). N–Nil, B–Bacteria, V–Virus. M–multiple organisms.

DISCUSSION

To our knowledge, this is one of the largest single–centre studies of CAP etiology in children from a resource–limited setting. Our data suggest that CAP is associated with a number of pathogens or combinations of viral and bacterial pathogens. Further, no single pathogen or combination could be related to disease severity. Our findings also confirm that infants <12 months old are particularly vulnerable in terms of disease severity and outcome.

As expected, *S. pneumoniae* was the predominant isolate in NPA by culture as well as PCR, although mere detection does not establish a causal role. We could not do serotyping due to resource constraints. It can be argued that the isolation rate by culture in our cohort is lower than expected [26,27], especially as PCR identified *S. pneumoniae* much more frequent-ly. It is possible that clinical pneumoniae on routine culture. The major difficulty in attributing etiology to *S. pneumoniae* is its frequent presence in asymptomatic children also, although a similar argument could be raised for *S. aureus* too [28,29].

Detection of multiple pathogens in NPA by PCR makes it difficult to ascribe a causal role to any one organism. Our culture and PCR data also suggest that nasopharyngeal specimens may perhaps be inappropriate for confirming microbial etiology in CAP. Indeed, this is in concordance with several recent studies showing the presence of various viruses in asymptomatic children as well as those with upper respiratory tract symptoms [19,30,31]. It appears that even *M. pneumoniae* can be identified in the nasopharynx of healthy children [32].

Somewhat surprisingly, CMV was the most common virus in our cohort, where none had immune–suppressive therapy, known primary immune–deficiency and where the HIV prevalence during the study period is reported to be <0.25% in the community [33]. While CMV is well–recognized as a pathogen in these latter settings, its frequent occurrence in CAP raises the possibility that it may contribute to pneumonia pathogenesis singly or with other pathogens [34]. This novel finding also emphasizes that although PCR is highly sensitive, it can detect only those organisms that are looked for-a limitation that is being overcome by next generation sequencing. After CMV, RSV was most frequently identified as previously reported also [2] while Influenza A and B were less frequent. Unfortunately, even BAL samples in a limited number of children could not ascertain etiology as most children had multiple organisms. Further the time-lag between presentation and obtaining BAL samples in the majority of children raises the possibility that some of the organisms could represent secondary infection.

How to interpret the detection of multiple organisms in respiratory tract samples from a given child? It is possible that infection by one (potential) pathogen facilitates other pathogens, or that mild infection with one organism becomes more severe in the presence of additional organisms. This is well documented with Influenza infection [35,36] and suggested for other organisms also [2]. However, the pattern of PCR findings did not differ with disease severity which is in concordance with initial data from the PERCH project also [16]. In our cohort, a single organism (bacteria or virus) was identified by NPA PCR in only a minority of children. Further NPA data may be skewed on account of nasopharyngeal carriage. The limited BAL data suggests that S. pneumoniae, CMV, S. aureus and H. influenzae may be the dominant pathogens in severe cases of CAP. In children with fatal outcome, the same pathogens were identified along with RSV.

In the small number of positive blood cultures, *S. aureus* predominated, rather than *S. pneumoniae* or *H. influenzae*, expected in a vaccine–naïve pediatric population such as our cohort. Clinical experience suggests that *S. aureus* is frequently responsible for community acquired infections in India, although it has not previously been documented as the most frequent cause of bacteraemia in childhood pneumonia. In contrast, it is the most frequently recovered pathogen in parapneumonic effusions/empyema complicating pneumonia [37-39] and also commonly isolated in blood cultures from infants with bacteraemia [40]. Therefore it is reasonable to conclude that *S. aureus* may be an important pathogen in childhood pneumonia as well. However, international and national antibiotic treatment protocols for childhood CAP do not use specific antibiotics against this organism.

The data presented in this study raise some important points for further research on childhood CAP. First, the mere identification of organisms by highly sensitive techniques may not confirm etiology. Even comparing the yield among cases vs controls, as planned in the PERCH Project [41] can at best suggest an association, but not causation. In an individual child, even the presence of organisms commonly associated with pneumonia may be of limited value for predicting pneumonia severity/ outcome. The presence of potential pathogens in the respiratory secretions of apparently healthy children also raises the possibility that microbes may not be solely responsible for disease. It is likely that combinations of host immune status and/ or response to infection/inflammation tip the balance from asymptomatic colonization to disease in a given child.

Although this study had several methodological strengths limiting the risk of bias, it also had limitations. The disproportionately large number of severe and very severe pneumonia cases attest to greater enrolment through passive surveillance. Lack of controls is a limitation since it would have provided data on nasopharyngeal carriage of pathogens in asymptomatic/ healthy children in this population. Further, research team members could not be stationed in a given anganwadi throughout the study period, hence pneumonia incidence could not be calculated. We could perform only qualitative PCR, and that too in a small proportion (20%) of the cohort.

CONCLUSION

This large cohort study (CAPES) identified multiple pathogens in various biological samples of children with CAP. Our data suggest that it is difficult to attribute etiology to a single pathogen in the majority of cases as co–infection is common and independent of disease severity. Multiplex PCR proved to be highly sensitive in identifying potential pathogens from respiratory samples; but lacked specificity for establishing a causal relationship. A novel finding of CMV carriage/infection in nasopharyngeal secretions was observed. Our findings suggest that clinical practice guidelines for management of suspected bacterial pneumonia in developing countries should additionally consider anti–Staphylococcal therapy. Rational vaccination policies against *S. pneumoniae*, *H. influenzae* and (in the future) RSV could decrease overall burden of childhood pneumonia morbidity and mortality.

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Ethics: Approval was obtained from the Institutional Ethics Committees of PGIMER Chandigarh (No. 5769 dated 24 Nov 2009) as well as the Ministry of Health and Family Welfare, Government of India (No. 5/8/9/106/2010–ECD–1). Children were enrolled with written, informed consent of their parent/legal guardian.

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Authorship Declaration: JLM designed the study, established study procedures and data collection tools, supervised patient enrollment and data collection, participated in clinical care of patients, assisted with interpretation of radiographs, contributed to data management and analysis, wrote the manuscript and finalized it. SS confirmed the study design and procedures, supervised data collection, supervised clinical management of patients, provided critical inputs to the manuscript, and finalized it. PR was responsible for bacterial culture including blood, NPA and BAL. EH was responsible for data management, data cleaning, data analysis and statistics. SS–H: assisted with data analysis, data management, preparation of figures and provided critical inputs to the manuscript. AB: assisted with patient enrollment, clinical care and data collection. SY: assisted with data analysis, data management, and provided critical inputs to the manuscript. KSS was responsible for radiographic procedures and interpretation. BVRK was responsible for multiplex PCR in NPA and BAL samples. AN assisted with study design, secured funding, assisted with data management and analysis, provided critical inputs to the manuscript and finalized it.

Competing interests: The author completed the Unified Competing Interest form at www.icmje.org/coi_disclosure. pdf (available on request from the corresponding author). None of the authors has any competing interests to declare. BVRK is the Chairman and Managing Director of Xcyton Diagnostics Pvt Ltd.

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Evaluation of case definitions for estimation of respiratory syncytial virus associated hospitalizations among children in a rural community of northern India

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Siddhartha Saha, MD Public Health Specialist–Influenza Centers for Disease Control & Prevention Shantipath Chanakyapuri New Delhi–110021 India ssaha1@cdc.gov **Background** The burden estimation studies for respiratory syncytial virus (RSV) have been based on varied case definitions, including case–definitions designed for influenza surveillance systems. We used all medical admissions among children aged 0–59 months to study the effect of case definitions on estimation of RSV–associated hospitalizations rates.

Methods The hospital–based daily surveillance enrolled children aged 0–59 months admitted with acute medical conditions from July 2009–December 2012, from a well–defined rural population in Ballabgarh in northern India. All study participants were examined and nasal and throat swabs taken for testing by real–time polymerase chain reaction (RT–PCR) for RSV and influenza virus. Clinical data were used to retrospectively evaluate World Health Organization (WHO) case definitions (2011) commonly used for surveillance of respiratory pathogens, ie, acute respiratory illness (WHO–ARI), severe ARI (SARI) and influenza–like illness (ILI), for determination of RSV–associated hospitalization. RSV–associated hospitalization rates adjusted for admissions at non–study hospitals were calculated.

Findings Out of 505 children enrolled, 82 (16.2%) tested positive for RSV. Annual incidence rates of RSV–associated hospitalization per 1000 children were highest among infants aged 0–5 months (15.2; 95% confidence interval (CI) 8.3–26.8), followed by ages 6–23 months (5.3, 95% CI 3.2–8.7) and lowest among children 24–59 months (0.5, 95% CI 0.1–1.5). The RSV positive children were more likely to have signs of respiratory distress like wheeze, chest in–drawing, tachypnea, and crepitation compared to RSV–negative based on bivariate comparisons. Other less commonly seen signs of respiratory distress, ie, nasal flaring, grunting, accessory muscle usage were also significantly associated with being RSV positive. Compared to the estimated RSV hospitalization rate based on all medical hospitalizations, the WHO–ARI case definition captured 86% of the total incidence, while case definitions requiring fever like ILI and SARI underestimated the incidence by 50–80%.

Conclusions: Our study suggests that RSV is a substantial cause of hospitalization among children aged <24months especially those aged <6 months. The WHO–ARI case definition appeared to be the most suitable screening definition for RSV surveillance because of its high sensitivity.

Globally, respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infection (ALRI) including bronchiolitis and pneumonia among young children [1,2]. Studies indicate that most children are infected by RSV in the first two years of life with infants bearing the highest rates of RSV–associated lower respiratory illness [3,4]. A recent meta–analysis estimated 3.4 million hospitalizations and 66 000–199 000 RSV–associated deaths among children <5 years of age with ALRI, with 99% of the deaths occurring in developing countries [5]. While there are some studies on burden of pneumonia and viral etiology in India and other developing countries [2,6], recent data from a community–based and hospital–based studies have further emphasized the importance of RSV among children <5 years of age [7-9].

Systematic data are needed to better understand seasonality, burden and mortality associated with RSV infection in children. RSV infection has a different clinical presentation, age distribution, risk factors, and seasonality compared to influenza infection and requires studies specifically designed to detect and evaluate RSV [3,4]. For example, RSV illness may present without fever particularly among infants, whereas influenza is more likely to present as a febrile illness and thus, fever may be included in the case definitions [10]. However, existing surveillance networks for influenza, with protocols and case definitions designed for influenza have also often been used to generate burden estimations for RSV [11]. Thus, there is a need to identify appropriate case–definitions for epidemiologic field studies to accurately estimate the RSV burden among children.

The presence of a broad platform to estimate the rates of hospitalized influenza which captured all–cause hospitalization in a well–defined population with health demographic surveillance system [12] enabled us to evaluate the sensitivity and specificity of different case definitions and RSV burden among children <5 years in a rural setting in northern India. The current paper utilizes data from this hospital–based surveillance study to evaluate case definitions for RSV detection and the impact of choice of case definitions on RSV hospitalization rate estimates among children aged <5 years in a rural setting in India.

METHODS

Study site

The Ballabgarh Health and Demographic Surveillance System (HDSS) site is about 40 km south of Delhi and comprised a population of about 90000 in June 2011 including 9500 children 0–59 months of age in 28 villages [13]. Based on health utilization survey of the site population conducted in April 2009, three public hospitals and 30 private facilities (ranging in size from 5–35 beds) in Ballabgarh and Faridabad towns were included for daily surveillance for patients from the catchment area seeking inpatient care [12,14]. Immunization coverage for EPI vaccines (BCG, DPT, OPV, Hepatitis B and Measles) provided through public health facilities was >95% in the study villages [13]; Hib vaccine was introduced into public health program in 2012–2013. Coverage for pneumococcal and rota vaccines are not known but likely to be low as they are available only in private facilities.

Enrolment and data collection

During July 2009 – December 2012, hospital–based daily surveillance–enrolled children aged 0–59 months from Ballabgarh–HDSS area who were hospitalized overnight with any acute medical illness or acute exacerbation of chronic illness at participating medical facilities [8,12]. Trained study physicians collected data using a standardized form on demographics, medical history and clinical symptoms by interview of the caregivers, and extracted data on clinical signs at admission from the medical record followed by clinical examination of cases for additional clinical information.

Study definitions

The presence of fever or key respiratory signs or symptoms was determined among all hospitalized children aged 0-59 months. Fever was defined as either measured temperature >38.0°C at admission or parental report of fever because antipyretic use is known to be common in the study community [15]. Key respiratory symptoms or signs were defined as parental report of cough or fast breathing or physician exam findings of tachypnea, crepitation, wheezing, nasal flaring, chest in-drawing, grunting, or stridor. Tachypnea was defined based on the definition used by the Indian Integrated Management of Neonatal and Childhood Illness (IMNCI) as ≥60 breaths/min in children aged 0–2 months of age, ≥ 50 breaths/min in children aged 2–12 months of age, and \geq 40 breaths/min in children aged 12 months -5 years of age [16]. Data on clinical signs and symptoms were used *post hoc* to classify each patient using standard case definitions specified by WHO (May 2011, see Box 1), ie, acute respiratory infection (ARI), severe acute respiratory infection (SARI), and influenza-like illness (ILI), and evaluated them for RSV positivity.

Specimen collection and laboratory methods

Nasal and throat samples were collected by a study nurse from all enrolled patients within 24 hours of admission to the hospital using polyester swabs; in infants only nasal swabs were collected. The swabs were placed immediately into viral transport media and transported on ice to laboratory on the same day for processing. Specimens were Box 1. Case definitions for respiratory syndromes [17,18]

ARI – acute respiratory infection (WHO, 2011):

Acute onset of at least one of the following four respiratory symptoms: cough or sore throat or shortness of breath or coryza and a clinician's judgment that illness is due to infection.

ILI – influenza–like illness (WHO, 2011):

An acute respiratory illness with onset during the last 7 days with measured temperature ≥38°C, AND cough. (Dropped sore throat).

ILI (old):

Sudden onset of fever (> 38° C) with cough or sore throat, in absence of other diagnoses.

SARI – severe ARI (WHO, 2011):

An acute respiratory illness with onset during the previous 7 days requiring overnight hospitalization that includes history of fever or measured fever of ≥38°C, AND cough, AND shortness of breath or difficulty breathing.

SARI (old):

Meets ILI (old) definition (sudden onset of fever (>38°C) with cough or sore throat) and has shortness of breath or difficulty breathing and requires overnight hospitalization.

Pneumonia (IMCI):

Fast breathing or chest indrawing

Severe pneumonia (IMCI):

General danger signs – Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor, or severe malnutrition

tested for RSV and influenza using US Centers for Disease Control and Prevention (CDC) real–time reverse transcription polymerase chain reaction (rRT–PCR) protocols, as described previously [8,12].

Data analysis

We assessed different signs and symptoms associated with RSV positivity using bivariate analysis for different age– groups and backward stepwise logistic regression adjusted for age–groups. We also assessed the ability of standard case definitions (ARI, SARI, ILI) for respiratory illness to capture RSV–associated hospitalizations by calculating sensitivity and specificity for each case definition using all RSV positive hospitalized patients as the gold standard. We assessed the impact of standard case definitions on average annual incidences of RSV–associated hospitalizations using available 3 calendar years' data from 2010 to 2012.

The population of June 2011 in the HDSS was considered the mid-term population denominator for calculations. Annual health utilization surveys were used to estimate the average proportion of hospitalization in enrolled facilities [14]. The annual hospitalization rates based on enrollment were adjusted for missed hospitalizations in non-study facilities and were multiplied by the positivity rate of the viruses to get an estimate of virus specific hospitalization rates. We calculated incidence rates for four age groups (0-5 months, 6–11 months, 12–23 months and 24–59 months) for RSV and influenza because clinical manifestations, as well as viral etiologies are likely to be different in these age groups. The average annual incidence was calculated separately for each case definition among all medical and respiratory admissions, to evaluate the effect of using different screening definitions on the estimations of RSV-associated hospitalizations. The data analysis was done using STATA 12 (College Station, Texas, USA) [17] and Micosoft Excel. A *P*-value of <0.05 was considered statistically significant for all analyses. The 95% confidence intervals (CI) for odds ratios, sensitivity and specificity were calculated.

RESULTS

Background characteristics

During the study period, 505 children aged 0–59 months from the HDSS area hospitalized with acute medical illness in the health facilities under surveillance were enrolled; of these 79.6% (402/505) were aged 0–24 months and 71.7% (362/505) were males (**Table 1**). RSV was detected in 82 (16%) hospitalized patients with 89% (73/82) of detections among children <2 years old (P<0.001). There was no significant difference in gender, time from symptom onset to specimen collection or any underlying medical condition among RSV negative and positive children (with the exception of chronic diarrhea observed among RSV negative children, data not shown). The RSV detections among hospitalized children occurred with seasonal peaks between September–October and then again in January–February of each year (data not shown).

Clinical characteristics

Among the enrolled children, 347 (68.7%) had some respiratory illness. Further, those with symptoms of cough (OR = 5.3, 95% CI 2.8 - 10.1) and fast breathing (OR = 3.9, 10.1)95% CI 2.4-6.3) were more likely to test positive than negative for RSV (Table 2). The presence of signs of wheeze, chest in-drawing, tachypnea, and crepitation had significantly higher odds of being RSV positive vs RSV-negative based on bivariate comparisons. Other less commonly seen signs of respiratory distress, ie, nasal flaring, grunting, accessory muscle usage were also significantly associated with being RSV positive. Stepwise backward logistic regression (Table 3) analysis of all clinical features identified the presence of cough, fast-breathing, crepitation and hypoxia as significant predictors for RSV-associated hospitalization, while history of fever and diarrhea were significantly associated with non-RSV-associated hospitalization.

– December 2012				
Characteristics (n, %)	Total (n = 505)	RSV+~(N=82)	RSV- (N = 423)	P value
Age group (months):				
0–5	114 (22.6)	35 (42.7)	79 (18.7)	<0.001
6–11	146 (28.9)	16 (19.5)	130 (30.7)	
12–23	142 (28.1)	22 (26.8)	120 (28.4)	
24–35	43 (8.5)	4 (4.9)	39 (9.2)	
36–59	60 (11.9)	5 (6.1)	55 (13)	
Sex:				
Female	143 (28.3)	24 (29.3)	119 (28.1)	0.834
Male	362 (71.7)	58 (70.7)	304 (71.9)	
Time from symptom onset to specimen collection:*				
0–2 days	127/468 (27.1)	16/79 (20.2)	111/389 (28.5)	0.497
3–4 days	135/468 (28.8)	26/79 (32.9)	109/389 (28.0)	
5–7 days	116/468 (24.8)	21/79 (26.6)	95/389 (24.4)	
8–10 days	39/468 (8.3)	9/79 (11.4)	30/389 (7.7)	
≥11 days	51/468 (10.9)	7/79 (8.9)	44/389 (11.3)	

Table 1. Characteristics of children <5 years of age enrolled for all cause hospitalization in Ballabgarh, Haryana, India from July 2009</th>– December 2012

*Data on 37 cases, including 3 RSV-positive cases, were missing.

Table 2. Age-specific clinical signs and symptoms significantly associated with laboratory-confirmed respiratory syncytial virus
infection among hospitalized patients <5 y of age, in Ballabgarh, India, July 2009 – December 2012; $(n = 505)^*$

	0—5 молтнз		6–23 months		24–59 months		0-59 months	
	RSV+ (n=35)	OR (95% CI)	RSV+ (n=38)	OR (95% CI)	RSV+ (n=9)	OR (95% CI)	RSV+ (n=82)	OR (95% CI)
Symptoms:								
Fever	27 (77.1)	0.6 (0.2–1.6)	32 (84.2)	0.8 (0.3–2.2)	9 (100.0)	_	68 (82.9)	0.8 (0.4–1.5)
Cough	32 (91.4)	4.4 (1.2–15.7)	32 (84.2)	6.5 (2.6–16.0)	6 (66.7)	1.6 (0.4–6.8)	70 (85.4)	5.3 (2.8–10.1)
Breathing difficulty	20 (57.1)	3.5 (1.5–7.9)	15 (39.5)	3.3 (1.6–6.9)	2 (22.2)	1.5 (0.3–8)	37 (45.1)	1.8 (1.1–2.7)
Nasal discharge	13 (37.1)	1.4 (0.6–3.1)	20 (52.6)	2.3 (1.1–4.5)	4 (44.4)	2 (0.5–8)	37 (45.1)	1.8 (1.1–2.9)
Sore throat (>2years)	0 (0)	_	0 (0)	-	2 (22.2)	1.5 (0.3–8)	2 (16.7)	1.4 (0.3–7.1)
Ear discharge	1 (2.9)	1.1 (0.1–12.9)	4 (10.5)	2.3 (0.7–7.6)	0 (0)	-	5 (6.1)	1 (0.4–2.7)
Fast breathing	18 (51.4)	2.9 (1.3-6.7)	18 (47.4)	6.1 (2.9–12.8)	3 (33.3)	3.8 (0.8–17.3)	39 (47.6)	3.9 (2.4–6.3)
Lethargy	9 (25.7)	1.5 (0.6–3.9)	3 (7.9)	0.3 (0.1–0.9)	3 (33.3)	1.2 (0.3–5)	15 (18.3)	0.7 (0.4–1.2)
Refusal to feed	15 (42.9)	1 (0.5–2.3)	10 (26.3)	0.6 (0.3–1.3)	3 (33.3)	0.8 (0.2–3.3)	28 (34.2)	0.8 (0.5–1.3)
Seizure	2 (5.7)	0.9 (0.2–4.9)	0 (0)	-	2 (22.2)	6.4 (1-41.4)	4 (4.9)	1.6 (0.5–4.7)
Unconsciousness	2 (5.7)	0 (0–0)	0 (0)	-	0 (0)	-	2 (2.4)	1.5 (0.2–11)
Vomiting	10 (28.6)	0.4 (0.2–0.9)	22 (57.9)	0.4 (0.2–0.8)	4 (44.4)	0.5 (0.1–2)	36 (43.9)	0.4 (0.2–0.6)
Diarrhea	13 (37.1)	0.5 (0.2–1.2)	16 (42.1)	0.2 (0.1–0.4)	1 (11.1)	0.2 (0-1.7)	30 (36.6)	0.3 (0.2–0.5)
Rash	1 (2.9)	2.3 (0.1–37.8)	0 (0)	_	0 (0)	_	1 (1.2)	0.3 (0–2.6)
Jaundice	1 (2.9)	1.1 (0.1–12.9)	0 (0)	-	0 (0)	_	1 (1.2)	0.7 (0.1–4.2)
Signs:								
Fever	1 (2.9)	0.2 (0–1.3)	10 (26.3)	1.8 (0.8–4)	6 (66.7)	5 (1.2–21.3)	17 (20.7)	1.1 (0.6–2)
Stridor	4 (11.4)	2.4 (0.6–10.3)	5 (13.2)	9.3 (2.4–36.5)	0 (0)	0 (0–0)	9 (11)	5.7 (2.2–14.8)
Nasal flaring	5 (14.3)	2.4 (0.6–8.9)	4 (10.5)	9.7 (2.1–45.2)	0 (0)	0 (0–0)	9 (11)	5.1 (2–12.9)
Chest in-drawing	13 (37.1)	5.1 (1.2–13.9)	6 (15.8)	3.7 (1.3–10.6)	0 (0)	0 (0–0)	19 (23.2)	5.7 (2.9–11.3)
Grunting	5 (14.3)	3 (0.8–12.1)	4 (10.5)	7.2 (1.7–30.3)	0 (0)	0 (0–0)	9 (11)	5.6 (2.2–14.7)
Accessory muscle use	5 (14.3)	4.2 (0.9–18.8)	1 (2.6)	0.8 (0.1–6.7)	0 (0)	0 (0–0)	6 (7.3)	2.5 (0.9–6.8)
Crepitation	21 (60)	2.9 (1.3-6.6)	17 (44.7)	5.0 (2.4–10.3)	4 (44.4)	5.5 (1.3–23.2)	42 (51.2)	5 (3–8.2)
Wheeze	24 (68.6)	5 (2.1–11.8)	10 (26.3)	2.8 (1.2–6.4)	2 (22.2)	2.2 (0.4–11.7)	36 (43.9)	4.5 (2.7–7.5)
Tachypnoea	25 (71.0)	1.4 (0.6–3.3)	16 (42.1)	1.9 (0.9–3.8)	1 (11.1)	0.6 (0.1–4.8)	42 (51.2)	2.2 (1.4–3.5)
Hypoxia*	8 (22.9)	1.5 (0.6–4)	8 (22.9)	2.6 (1.0-6.6)	1 (11.1)	2.8 (0.3–28.3)	17 (20.7)	2.5 (1.3–4.8)

OR – odds ratio, CI – confidence interval

*Defined as oxygen saturation <90% on room air or <95% on oxygen the rapy.

Table 3. Clinical predictors of respiratory syncytial virus
associated hospitalization among children aged <5 y by
stepwise backward logistic regression adjusted for age-groups*

0	0	5	001
		Odds ratio (95% C	l) <i>P</i> > z
		1.85 (1.13-0.46) 0.013
		0.4 (0.23-0.11)	0.001
thing		3.44 (2.26–0.73) <0.001
		0.62 (0.41-0.12) 0.021
feed		0.57 (0.39–0.1)	0.004
		0.07 (0.01-0.07	0.005
		3.13 (1.41–1.27	0.005
		2.73 (1.22–1.12) 0.014
ıse		0.22 (0.08-0.11) 0.003
		2.79 (1.81–0.61) <0.001
		2.71 (1.58–0.74) <0.001
	feed use	feed	ODDS RATIO (95% C 1.85 (1.13–0.46 0.4 (0.23–0.11) athing 3.44 (2.26–0.73 0.62 (0.41–0.12 feed 0.57 (0.39–0.1) 3.13 (1.41–1.27 2.73 (1.22–1.12 use 0.22 (0.08–0.11 2.79 (1.81–0.61

CI - confidence interval

*Age groups: 0–5 months, 6–11 months, 12–23 months and 24–59 months.

Case definitions

We then examined the sensitivity and specificity of standard case definitions (ARI, SARI, ILI) for detection of RSV– associated hospitalization (**Figure 1**). Among the standard case definitions, ARI had the highest sensitivity (87.8%) and specificity (40%) based on receiver–operating characteristics. All other case definitions (ILI, and SARI, (both old and revised 2011 versions) had lower sensitivity and variable specificity, with older the definition of SARI showing higher specificity). We also evaluated different clinical syndromes including IMCI definitions of pneumonia/severe pneumonia [18] and other syndromes. The sensitivity of IMCI either pneumonia or severe pneumonia was high (75.6%) but specificity was low (31.9%). Among other combination of symptoms and signs, we found history of cough or crepitation along with presence of any one of following– history of fast–breathing, breathing difficulty, nasal discharge, sore–throat, chest–in–drawing, wheeze or hypoxia, had high sensitivity (81 · 7%) and specificity (60%).

Burden of RSV in children

The average annual incidence of RSV–associated hospitalizations was found to be higher at $7 \cdot 4$ (95% CI: $4.9-10 \cdot 5$) per 1000 child–years in those 0–23 months as compared to 0.5 (95% CI 0.1–1.5) among 24–59 months population signifying that most of burden of RSV–associated hospitalization is among children under two years of age. Further breakdown of the age–specific annual incidence of RSV– associated hospitalization per 1000 children revealed that the highest rate occurred in young infants 0–5 months (OR=15.2, 95% CI 8.3–26.8), followed by 6–23 months (OR=5.3, 95% CI 3.2–8.7) with comparable rates for the 6–11 months and 12–23 months age groups (**Figure 2**). Incidence rates for influenza were lower across all age groups.

Impact of case definitions on RSV burden

We assessed the impact of the use of different standard case definitions on RSV burden estimates by comparing the definitions with RSV hospitalization based on all–cause hospitalization (**Table 4**). Use of the ARI case definition among hospitalized children would have detected 90% and 86% of the RSV–associated hospitalization rates in children aged <2 years and <5 years, respectively. In contrast, use of definitions which require presence of fever and most commonly used for influenza surveillance platforms, ie, SARI or ILI definitions, (both old and revised) would have under estimated RSV burden by as much as 50–85% in both <2 as well as <5–year age groups (**Table 4**).

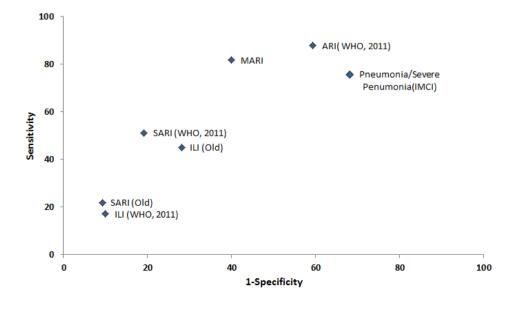


Figure 1. Receiver operator characteristic (ROC) chart for screening definitions for respiratory syncytial virus associated hospitalization with 1–specificity on x-axis and sensitivity on y-axis. Each dot represents the sensitivity and 1–specificity of the case definition for detection of RSV–associated hospitalization. See **Box 1** for case definitions details of each syndrome. Saha et al.

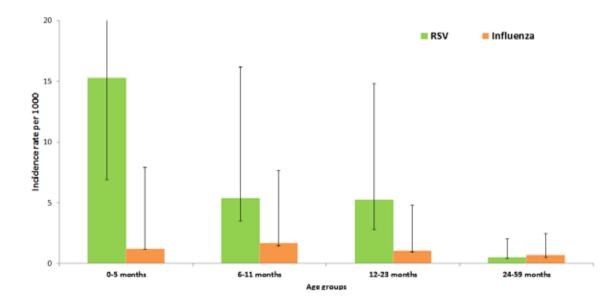


Figure 2. Age–specific incidence rates using all–cause hospitalization for respiratory syncytial virus (RSV) and influenza–associated hospitalization rates in north India (2009–2012). The age groups are on the x–axis and incidence rate of RSV–associated hospitalization per 1000 children denoted on the y–axis. Green and orange colored bars denote incidence rates of RSV and influenza associated hospitalizations respectively with error bars for 95% confidence intervals.

Population under surveillance	Under-2 years (N = 3956)				Under-5 years (N = 9740)			
Case definitions	No. met case definition	No. of RSV positive cases (%)	Incidence Rate (IR)†	IR under–esti- mation (%)	No. met case definition	No. of RSV positive cases (%)	IR†	Under–estima- tion IR (%)
All Medical	386	67 (17)	7.4	NA	484	74 (15)	3.2	NA
ARI (WHO)	239	60 (25)	6.6	-10%	299	64 (21)	2.8	-14%
SARI (WHO)	90	34 (38)	3.8	-49%	107	35 (33)	1.5	-53%
SARI (Old)	35	10 (29)	1.1	-85%	41	11 (27)	0.5	-85%
ILI (WHO)	37	10 (27)	1.1	-85%	54	14 (26)	0.6	-81%
ILI (Old)	106	26 (25)	2.9	-61%	139	32 (23)	1.4	-57%

Table 4. Effect of screening case definition on respiratory syncytial virus (RSV) associated annual hospitalization rates (2010–2012)*

ARI - acute respiratory illness, SARI - severe acute respiratory illness, ILI - influenza-like illness, WHO - World Health Organization

*For incidence rate calculations data for full calendar years were used. Data imputed for 6 weeks surveillance gap between 31 January 2012 and 13 March 2012.

†Per 1000 age-specific population.

DISCUSSION

The uniqueness of this study based on a comprehensive surveillance system designed to capture all–cause hospitalization in a well–defined population, together with the availability of highly sensitive molecular testing for RSV allowed us to estimate RSV–associated the hospitalization rates among children aged <5 years in rural northern India [8,12]. Most studies estimating RSV–associated burden rely on existing surveillance platforms for influenza in developing countries [11,19]. A very important aspect of our study was that we were able to evaluate the impact of using different case definitions on burden estimation. We provided evidence that the WHO–defined ARI case definition has the highest sensitivity for RSV–associated hospitalization and demonstrate the limitations of definitions like ILI and SARI commonly used for influenza surveillance. We found that testing only children meeting the SARI and ILI definitions would have under–estimated the burden of RSV–associated hospitalization by almost 50–85%, although specificity would have been significantly higher with the latter case definition. Several case definitions, including ARI, have been used in studies for RSV burden estimation in many countries [11,19-22]. This highlights the importance of the use of a sensitive case definition for surveillance of RSV to avoid underestimation of the burden.

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The all-cause hospitalization surveillance also allowed us to compare the symptoms and signs of hospitalized children with or without RSV and thereby identify the clinical predictors for RSV-associated hospitalization in children; this would not have been possible if only standard case definitions were used to identify potential RSV patients. We found that the presence of cough, fast-breathing, crepitation and hypoxia are independent predictors of RSV infection. Of note, Durani et al. (2008) in their study among children hospitalized with ARI found the combination of cough, wheezing and retractions to be good clinical predictor for RSV infection [23]. We found that even though fever is a common presenting symptom and sign among children being hospitalized, it is not a good predictor of RSV-associated hospitalization in this population. The use of history or presence of fever in screening case definitions lowers the sensitivity of the definition. We also observed that two-thirds of hospitalized patients had some respiratory symptoms, suggesting that a very high proportion of hospitalizations are due to respiratory symptoms in rural India. This observation corroborates previous findings that ARI is a significant cause of morbidity in the developing world [4,24,25].

We found substantial incidence of RSV-associated hospitalization in the study community especially among <2year old children. The RSV-associated incidence of hospitalization per 1000 child-years was 3.2 among <5-year children, and 7.4 among <2-year children, with highest incidence rate of 15.2 per 1000 child years among infants 0-5 months, which is similar to findings of an earlier community-based study from this area [7]. RSV-associated hospitalization rates among children <5 years observed in our study were also comparable to what has been observed in Kenya (2.9/1000 child-years) and Guatemala (2-13.7/1000 child-years), although lower than in Thailand (9.8/1000 child-years), Indonesia (34/1000 child-years), Nigeria (94/1000 child-years) [20-22,26]. The highest risk group for RSV-associated burden was infants 0- to 5-month old, which was also observed in Thailand (15.4/1000 child-years), Indonesia (41/1000 child-years), Hong Kong (<6m, 23.4-31.1/1000 childyears), Guatemala (5.9-45.9/1000 child-years), Kenya (11.0/1000 child-years) and Nigeria (116/1000 childyears). Studies from Brazil, USA and Korea have established that infants are at high risk of RSV-associated burden both in terms of incidence in community and proportion of hospitalization [19-22,27-31]. Even though the rates of RSV-associated hospitalization vary in different countries, most of the burden is observed among children aged <2 years, therefore studies focusing on RSV–associated morbidity and mortality or high–risk group for RSV infections may consider children aged <2 years. Also, prioritizing this age–group for any preventive measure would likely have profound effect on prevention of RSV– associated hospitalization and deaths in India and other developing countries [32,33].

The study's limitations include first that it was designed to address influenza-associated burden, so data on variables such as gestation at birth were not collected; this data might have allowed us to also understand some of the risk-factors for RSV infection. Second, the active surveillance at health facilities (which were almost 30 plus facilities) did not capture all hospitalizations for the denominator population, and we had to make adjustments in rates of hospitalization using HDSS survey results. It is plausible that children seeking care at participating hospitals may be different from those who did not seek care in these hospitals, thus biasing the incidence rates for RSV. Third, there is a possibility that we have under-estimated the burden of RSV-associated hospitalization as some children might not have been hospitalized in spite of being diagnosed with severe respiratory illness [11,24]. Despite these limitations, we believe that this study enabled us to understand the effect of surveillance case definitions on population-based rates of RSV hospitalization in northern rural India. However, due to the study design where we captured all cause medical hospitalization instead of ILI or SARI, we are in unique position to not only address the burden of RSV, but also assess various screening case definition for RSV-associated hospitalization. Analysis of this broad platform for RSV case definition assessment allowed us to recommend the WHO-defined ARI case definition as the most appropriate screening case definition for RSV among those considered.

CONCLUSION

In conclusion, we observed that RSV is a substantial cause of hospitalization among children aged <2 years, and especially among infants aged <6 months. This is true regardless of the screening definition used, even though rates may be underestimated if an insensitive screening definition is used. These data will help support public health strategies and interventions, targeting young children to reduce the overall RSV–associated morbidity and mortality among children in the developing world.



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Authorship declaration: SS, RBL, AK, and SB conceptualized the study design. SKR, and SB managed the surveillance platform. BG, AC, and SB performed sample processing and viral testing. SS and RBL analyzed the data and wrote the first draft. AK, MKI, SIG, PS, MSC reviewed the results and helped writing the manuscript. All authors reviewed the manuscript.

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

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