Vol 1. No. 2
December 2011
ISSN 2047-2978

journal of global health

In the Millennium Development Goals, the United Nations set the targets to reduce the mortality rate in pre-school children by two-thirds (Goal 4), and to decrease maternal death ratios by three-quarters between 1990 and 2015 (Goal 5). Recent estimates suggest that every year there are still up to 400 000 maternal deaths occurring worldwide, and up to 9 million deaths in children younger than 5 years of age. Among mothers, about 10% of deaths are thought to be directly attributable to infection or sepsis, while among children infectious diseases still cause 60–70% of all deaths. The group of children who are particularly vulnerable to infections are neonates – newborn babies in their first month of life. Up to 900 000 of neonates are still thought to be dying each year in the world as a direct consequence of infection or sepsis.

The photograph is the courtesy of Dr David Hipgrave, personal collection

Journal of Global Health: The Mission Statement

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

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

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

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

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

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

March 7, 2011

The Editors, *Journal of Global Health*

EDITORIAL

Reducing the burden of maternal and neonatal infections in low-income settings

Igor Rudan, Evropi Theodoratou, Harish Nair, Ana Marušić, Harry Campbell

Maternal and neonatal infections remain responsible for up to 1 million deaths each year globally. Current approaches to prevention, early diagnosis and appropriate management are limited by difficulties in developing vaccines against the main pathogens, or alternatively diagnosing the infections accurately and managing them appropriately and effectively in low-resource settings. We propose that short-term priorities should focus on promotion of evidence-based, cost-effective home care practices to prevent maternal and newborn infections, with increased coverage and improved quality of maternal and neonatal care interventions. Longer-term strategic priorities will ultimately need to focus on the development of vaccines and point-of-care diagnostic tests. Diagnostic tests should help establish the aetiological diagnosis and inform treatment decisions. They will also need to be deliverable, affordable, sustainable and acceptable in low-resource settings. The cost-effectiveness of maternal immunization in the protection of neonates will also need to be established.

Millennium Development Goals 4 and 5 require a substantial reduction in child and maternal mortality, respectively, between 1990 and 2015 (1). Infectious diseases are still the major cause of mortality in both population groups. Maternal and neonatal infections remain responsible for more than 1 million deaths each year (2–6), i.e. 10–15% of all maternal and child deaths globally. The large majority of these deaths occur in low-income settings, among mothers and children that do not have access to the (underdeveloped) health systems of their countries (2–5). Maternal deaths are clustered around labour, delivery and the immediate postpartum period. HIV/AIDS is a leading cause of death where HIV-related mortality rates are high, and a number of other infectious agents also play a significant role (3). Newborn infections can be divided into early (within the first week of life) and late infections (during weeks 2–4). The former are frequently related to labour and childbirth and are caused by an entirely different spectrum of pathogens than the late neonatal infections (7–9).

Current approaches to prevention, early diagnosis and appropriate management of maternal and neonatal infections globally are limited by difficulties in developing vaccines against the leading prevalent pathogens, or alternatively diagnosing them accurately and managing them appropriately in low-resource settings (4–9). Implementation of existing diagnostic tests and treatments from industrialized countries is challenging in low-resource settings due to their high cost, complexity, infrastructure requirements, inadequately trained end users, low acceptability among health personnel, affected mothers and newborns' parents, risk of obtaining blood samples for diagnostic testing in unhygienic settings and lack of appropriate quality control measures (5–7).

The information on causal infectious agents in low income settings is available mainly from hospital-based studies, which are not always representative of hospital care at a national level, and may also have limited relevance to settings where most children are born at home (6–8). It is likely that the etiological spectrum also varies significantly across geographic regions (7–9). However, the information on geographic differences in low-income countries is at present very limited. Maternal infections can be caused by a number of bacterial, viral and parasitic agents (2). In neonates, the available data indicate that Gram-negative rods are the major cause in early neonates (the first week of life),

where they may cause up to three in every four infections (7,8). *Klebsiella spp.*, *Staphylococcus aureus*, *Escherichia coli* and group B *Streptococci* are thought to be the leading causes in the early neonatal period, when most of the deaths occur (7,8). Many of those infections may be environmentally acquired because of unhygienic delivery practices in resource-poor settings rather than being passed on by mothers, which may also explain the predominance of Gram-negative infections among home-born infants (7,8). Their importance decreases in the late neonatal and post-neonatal periods when Gram-positive *cocci* (primarily *Streptococcus*) cause about 2 in every 3 infections (6–9).

Several studies in resource-poor settings have investigated the effectiveness of interventions to prevent and treat maternal and neonatal infections at both community and facility level. It has been reported that skin application of sunflower seed oil provides cheap, safe and effective protection against nosocomial infections in hospitalized preterm neonates and infants (10). Once the infection has developed, the standard treatment approach is oral (for mothers) or parenteral (for newborns) antibiotic treatment. However, a number of very complex and context-specific issues must be considered when selecting the appropriate antimicrobial regimens in the resource-poor settings where most deaths occur. The challenge is to choose a regimen that is effective against the causative pathogen yet affordable in that context, safe for the mothers, foetuses and newborns, and feasible to deliver reliably in the hospital or community setting, as appropriate (11).

Parenteral (intramuscular) regimens for newborns that are currently recommended by the World Health Organization and national paediatric associations comprise a combination of procaine penicillin G (or ampicillin) and gentamicin, or third generation cephalosporins given alone, which are safe and retain efficacy when administered at extended intervals (11). Attempts to estimate the effect of antibiotic use on the reduction of maternal and neonatal mortality in community settings in low income countries have encountered large methodological limitations, but have concluded that all available data suggest a substantial benefit associated with these case management approaches (12). However, recent reports based on hospital-based data suggest alarming rates of laboratory antimicrobial resistance to ampicillin and gentamicin, the first-line antimicrobial agents recommended for the treatment of serious infections in young infants. Significant in-vitro resistance to cotrimoxazole among all the major pathogens and to gentamicin and third generation cephalosporins among *Klebsiella spp*. and emerging resistance in *E. coli* are a cause for increasing concern (13).

The strategy promoted by the GAVI Alliance is to save children's lives and protect their health by increasing access to immunisation in the world's poorest countries, particularly through acceleration of the uptake and use of underused and new vaccines (14). The successful outcome of this approach is less sensitive to obstacles in accessing health care system throughout the childhood than some other proposed approaches, so it is continuously gaining support and improving child health worldwide. Passive transfer of antibodies from the mother coupled with the immature immune system of neonates acts to reduce the effectiveness of a vaccination strategy in this age period, although this is not true in all cases (e.g., maternal tetanus and influenza immunization). Prevention of microbial infection is a priority, because globally, a majority of neonates still die at home, and many of the deaths are thought to be due to infection (2). Maternal immunization probably offers the most promising means of achieving this objective in the longer term. However, vaccines against key pathogens involved in neonatal sepsis are still a long way from final phases of product development and licensing (15,16). It is likely that improving the diagnosis and treatment of neonatal infections will be a central approach to reducing deaths from neonatal infections in the medium term. Therefore, the slow and difficult route through improving local health systems and attention to specific contexts will be required to tackle neonatal infections globally (15,16).

> Considerable uncertainty still surrounds our current understanding of the epidemiology, aetiology, and effectiveness of available interventions, investment priorities, appropriateness of health policies, and true potential of new preventive interventions and diagnostic tools to address the burden of maternal and neonatal infections globally.

Implementation of existing diagnostic tests and treatments from industrialized countries is challenging in low-resource settings due to their high cost, complexity, infrastructure requirements, inadequately trained end users, low acceptability among health personnel, affected mothers and newborns' parents, risks associated with obtaining blood samples for diagnostic testing in unhygienic settings, and lack of quality control. We propose that short-term priorities should focus on promotion of cost-effective home-based care practices to prevent maternal and newborn infections, with increased coverage and improved quality of maternal and neonatal care. Longer-term strategic priorities will ultimately need to focus on the development of vaccines and point-of-care diagnostic tests for maternal and neonatal infections. Diagnostic tests should help establish the aetiological diagnosis and inform treatment decisions. They will also need to be deliverable, affordable, sustainable and ac-

Implementation of existing diagnostic tests and treatments from industrialized countries is challenging in low-resource settings due to their high cost, complexity, infrastructure requirements, inadequately trained end users, low acceptability among health personnel, affected mothers and newborns' parents, risk associated with obtaining blood samples for diagnostic testing in unhygienic settings, and lack of appropriate quality control measures.

ceptable in low-resource settings. Cost-effectiveness of maternal immunization in protection of neonates will also need to be established (15,16).

The latter strategy may have different stages. In an earlier stage, tests that could separate viral and bacterial infections, and identify children who need treatment, could be considered a priority for development and implementation. In the longer term, tests that could identify a specific causal pathogen and predict antibiotic resistance may become a focus of interest. The development of such tests should maximize the effectiveness of the chosen treatment, whilst minimizing the emerging problem of antibiotic resistance. Biomarkers are very rarely used in low resource settings, because most of the cases and deaths occur at home and medical laboratories do not even have the most basic facility for blood culture. At this point there is no specific guideline for the use of biomarkers for maternal or neonatal infections. Even if they became available in high-income countries, the biomarkers will not be easily transferable to low resource settings due their high cost and complexity. A new generation of diagnostic tests will be needed at the point-of-care in low resource settings to diagnose neonatal infections, identify responsible pathogens, guide the choice of an appropriate treatment regimen, monitor effectiveness of interventions and determine drug resistance. One of the anticipated uses of the test is also for identifying those neonates that are severely ill and need to be immediately referred to the hospital for intensive care treatment. But in spite of the severe shortage of effective new diagnostics suitable for low-resource settings, there are very few research initiatives to address this problem. This may be due in part to a scarcity of information on the potential health impact and performance of essential diagnostics, and to the low return on investment in diagnostics perceived by the industry (15,16).

Considerable uncertainty still surrounds our current understanding of the epidemiology, aetiology, and effectiveness of available interventions, investment priorities, appropriateness of health policies, and true potential of new preventive interventions and diagnostic tools to address the burden of maternal and neonatal infections globally (2–9). The potential health impact of new diagnostic tools for neonatal infections is uncertain and needs to be modelled based on available information.

In this issue, several papers aimed to review the spectrum of pathogens that threaten maternal and newborn lives in low and middle income countries: Palani Velu et al. focused on maternal bacterial and viral infections (17), Roberts et al. on maternal parasitic infections (18) and Waters et al. on neonatal infections (19). In addition, Saha et al. (20) reviewed the existing biomarkers and diagnostic tests that could be used in low resource settings, while Rubens et al. and Wagner et al. reviewed diagnostic markers that are still in the pipeline and that could be valuable in the diagnosis of neonatal infections, alongside their potential for multiplexing and laboratory requirements (21–22). Understanding the potential impact of new diagnostic tools could encourage donors, researchers, technology developers, policy-makers, international organizations and other stakeholders to enhance their collaboration and focus their efforts, which should in turn lead to a much needed reduction of child deaths from neonatal infections.

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Africa

Cape Verde's Pedro Verona Pires awarded Mo Ibrahim African leadership prize

Cape Verde's former president Pedro Verona Pires won the US$ 5 million (€ 3.8 million) "African leadership prize" awarded by the Mo Ibrahim Foundation. The prize was created in 2007, it is worth US$ 5 million (€ 3.8 million) over 10 years and then US$ 200 000 (€ 154 333) annually for life thereafter. Previous winners included Mozambique's former president Joaquim Chissano and Botswana's Festus Gontebanye Mogae, while Nelson Mandela of South Africa was named an honorary laureate in 2007. This year the prize was given to Mr Pires for transforming his small country into a model of democracy and stability and then deciding to step down after his second term. Speaking for *The Guardian*, Salim Ahmed Salim, the chair of the prize committee, has said that "...under 10 years as president, the nation became only the second African country to graduate from the United Nation's least-developed category and has won international recognition for its record on human rights and good governance". Pires was appointed first prime minister of independent Cape Verde in 1975, and he remained in this post for 16 years. He lost his country's first democratic elections in 1991, but was elected again in 2001 and then re-elected in 2006. For the past two years the Foundation, set up by a Sudan-born billionaire Mo Ibrahim, did not award a prize as no leaders met the criteria for promoting development and democracy and for handing over power peacefully.

Vaccine introduction reduced pneumonia infections in Kenya by more than two-thirds

In a recent study, conducted by the Kenya Medical Research Institute Wellcome Trust Research Programme, pneumonia infections in Kilifi, Kenya, have dropped by 70% since the introduction of the pneumococcal vaccine. Earlier this year, in February 2011, Kenyan president Mwai Kibaki made the pneumococcal vaccine available to all Kenyan children. The vaccine is now freely available in about 3200 health facilities across Kenya that offer immunization. The vaccine targets infants in their first year of life and is given in three doses. Beth Mugo, a minister for public health, urged mothers to ensure that their children have the course completed to prevent resistance to the vaccine. This is of particular importance because early data showed that more than 20% of the vaccinated children did not complete the full course. Annually, the government will be contributing 72 million Kenyan shillings for the vaccine introduction. As the vaccine is now available throughout the country, the local experts believe that the results of the study are indicative for the country as a whole.

H3Africa aims to bring research capacity in genomics to the poorest continent

H3Africa stands for the "Human Heredity and Health in Africa". This welcome initiative aims to facilitate a contemporary research approach to genetic and environmental determinants of common diseases, resulting in an improved health among African populations. This should be achieved through the development of the necessary expertise among African scientists, and also establishing networks of African investigators. Current genomic research in wealthy countries is focused on developing tools for early and more accurate diagnosis, the development of new drugs and, potentially, personalized medicine – which has become a term describing the idea of systematic use of information about each individual to select or optimize the care provided to each patient individually. However, most African countries are being left out of the ongoing genomic revolution. The sponsors behind this initiative are the African Society of Human Genetics, the National Institutes of Health in the USA and The Wellcome Trust in the UK.

BMJ's publication on the cost of Africa's doctor brain drain appears flawed

In 2010, the World Health Assembly adopted the first "Code of Practice on the International Recruitment of Health Personnel". The idea behind this code was to recognise problems associated with doctor migration, implications on health systems in low resource settings, and to call on wealthy countries to provide financial assistance to source countries affected by health worker losses. In late November this year, a study published by BMJ claimed Sub-Saharan African countries that invest in training doctors "*have ended up losing US$ 2 billion as the expert clinicians leave home to find work in more prosperous developed nations*", as Reuters subsequently reported. But only weeks later Michael Clemens from the Center for Global Development ridiculed the simplistic approach to that calculation, pro-

viding six important arguments that all relate to the complexities of assessing the costs and benefits of highly skilled workers to their home nation – none of which had been considered in the original article, and all of which would probably entirely change the conclusions.

Lead poisoning epidemic in Nigerian villages

United Nations reported that more than 40 villages in Nigeria have been presenting cases of lead poisoning and called for an increase in preventive measures. The World Health Organization (WHO) has been assisting the Nigerian Government in dealing with the epidemic. WHO recommended strengthening the capacity to diagnose and treat the illness and ensuring de-contamination. WHO also warned about mining practices which are thought to be causing the sickness, with ore processing activities and storage of ore materials too close to the villages, using the obsolete practices with produce too much dust, and failure to remove contaminated clothes and wash before returning home. Lead poisoning damages the nervous system and causes brain and blood disorders, with long-term and expensive treatment with chelating agents required, which eventually remove heavy metals from the body. According to WHO, children in several villages in Zamfara state already require chelation therapy. Since the problem was discovered last year, nearly US$ 2 million (€ 1.5 million) has been provided by the UN Central Emergency Response Fund (CERF) to WHO and UNICEF to provide treatment, train doctors, provide diagnoses and raise awareness about the hazards of lead.

Asia

Afghanistan's largest mortality survey highlights improved maternal health

The Afghanistan Mortality Survey (AMS) was completed in 2010 as a part of the worldwide Demographic and Health Surveys (DHS) project. The survey showed a significant decrease in maternal mortality – to about 500 deaths per 100 000 live births. This is a truly significant decrease – down from 1800 per 100 000 live births in the UN's 2005 report. The AMS report suggests the decrease could be linked to the increased levels of antenatal care received by pregnant women. In the 36–59 months preceding the survey, 57% of women received antenatal care from a skilled provider, which rose to 68% of all pregnancies over the 12 months prior to the AMS survey. However, the report concedes that there is still a lot of work to be done, especially in regards to access to health care for women. The report found that 70% of women highlighted lack of money and distance to health care facilities as major barriers to accessing antenatal care.

MSF's outrage over CIA's fake vaccination campaign serving secret operations in Pakistan

As revealed by *The Guardian*, the international medical aid charity Médecins Sans Frontières (MSF) have lashed out at the CIA for using "...a fake vaccination programme as a cover to spy on Osama bin Laden". MSF said that this episode could threaten life-saving immunisation work around the world. The international medical aid charity added that this "...ploy used by US intelligence was a grave manipulation of the medical act". The CIA recruited a Pakistani doctor and health visitors before the operation that killed Bin Laden in Abbottabad, in northern Pakistan, to confirm that the al-Qaida leader was indeed living in the compound. The doctor set up a vaccination drive for Hepatitis B in the town, to gain entry to the Bin Laden compound and obtain DNA samples the residents. Speaking for *the Guardian*, a senior US government official defended the practice, saying that it had been intended as "...an actual vaccination campaign conducted by real medical professionals". Later in the year, a team from the non-governmental organisation Save the Children needed to evacuate from its operations site in Pakistan amid safety concerns.

50th anniversary of universal health care in Japan

In April, Japan marked the 50th anniversary of universal health care. Since its introduction, Japan became a leading nation in several health metrics, most notably longevity. To mark this anniversary, *The Lancet* published a series of six theme papers and eight comments by Japanese academics. According to *The Lancet*, as they describe Japan's actions and provide an opportunity to translate that experience to other settings, the invited theme papers resemble "...finely crafted netsuke (fasteners): both functional and provoking reflection".

A study reminds of a less prominent cause of malaria

The most common form of malaria in Africa, which is caused by *Plasmodium malariae*, has been the subject of intense research interest and investments of the Global Fund and other stakeholders. However, a less dangerous form of the disease – the one caused by *Plasmodium vivax* – is still very prevalent or endemic in large parts of South Asia and Latin America. Recently, a new global map of the *P. vivax* malaria parasite has been revealed. It showed that the disease is endemic in substantial parts of the world. Kevin Baird, a researcher working with the Eijkman-Oxford clinical research unit in Indonesia, said that all the new information increasingly showed that *P. vivax* was a bigger threat than generally thought. Primaquine is the only treatment for P. *vivax*, while all the current vaccine efforts are targeting P. *falciparum*.

Bangladesh plans to immunize 90% of children with major vaccines by 2016

Among six large populous countries eligible for GAVI support, Bangladesh earned recognition as the best performer in immunization coverage, after reducing the number of unimmunized children by more than 50% over the past four years. Bangladesh's Prime Minister Sheikh Hasina expressed her firm commitment to achieving the Millennium Development Goals in different sectors in Bangladesh, including child health. She said that 80% of children in Bangladesh have already been brought under the immunization programs and her current plan is to increase the coverage to 90% by 2016. UN honoured Sheikh Hasina by giving her Millennium Development Goal (MDG) Award last year.

Australia and Western Pacific

Kevin Rudd summarizes four years of foreign policy achievements

In November this year, the federal government of Australia completed their fourth year in charge, which also included the decisions made on foreign policy. The present minister of foreign affairs, Mr Kevin Rudd, gave a speech to the Australian Institute of International Affairs, outlining the challenges faced, achievements and visions of his government's foreign policy. The major focus of the speech was on the importance of Australia being positive, outward looking and globally engaged as a country. In his visions, Mr Rudd laid out 10 key goals to be focused on in Australia's foreign policy. Mr Rudd mentioned how in 2006 and 2007 Australian support for the Global Alliance for Vaccines and Immunisations (GAVI) funded the vaccination of 500 000 children against disease and how his government supported the further vaccination of 1.1 million children by the end of 2010 and pledged to vaccinate further 7.7 million by 2015. Australia also committed heavily to the Global Partnership for Education, which resulted in over 2 million children being enrolled and completing primary education. Mr Rudd also gave notice to Australia having been one of the largest bilateral donors of humanitarian aid in the recent Horn of Africa crisis.

Priority actions to tackle non-communicable disease (NCD) pandemics

In April, *The Lancet* published an important series of papers, led by Auckland-based Dr Robert Beaglehole on behalf of the Lancet's NCD Action Group and NCD Alliance. The series was published ahead of the UN's High-Level Meeting on Non-Communicable Diseases (NCDs). The authors proposed "...five overarching priority actions for the response to the crisis leadership, prevention, treatment, international cooperation, and monitoring and accountability and the delivery of five priority interventions: tobacco control, salt reduction, improved diets and physical activity, reduction in hazardous alcohol intake, and essential drugs and technologies". The priority criteria were their health effects, cost-effectiveness, low costs of implementation, and political and financial feasibility. Tobacco control was seen as the most urgent priority, while an estimated global commitment of about US$ 9 billion (€ 7 billion) per year would be required to bring enormous benefits to social and economic development and to the health sector.

Australia's Prime Minister joins The Gates Foundation in fight against polio

Polio has not been diagnosed in Australia for 40 years, but three of the four countries where it is still endemic – Nigeria, Pakistan and India – are members of the Commonwealth. This is why Australia's Prime Minister Julia Gillard chose to address the polio initiative, among other topics, at the Commonwealth Heads of Government Meeting earlier this year. She also published a joint opinion piece with Bill Gates in the Fairfax papers on the final push to eradicate polio earlier this year. Helen Evans, from the GAVI in Ge-

neva, said for the *ABC's The News Today* that she expected the Commonwealth Heads of Government Meeting to pressure countries where the disease still exists to act and eradicate it. Up until October 2011, the four countries recorded 429 new cases, which is down from 706 last year, but given that it is a highly infectious disease, the world cannot relax until it is fully eradicated. Complacency could see hundreds of thousands of new cases if immunization efforts were relaxed. Ms Evans added that The Bill and Melinda Gates Foundation have already put a huge amount of money into polio and that they were now "... calling on governments to join with them for this last piece of the fight".

Australian health official managed to misappropriate US$ 16 million intended for charities

According to Sydney's *Morning Herald*, an Australian health official allegedly managed to steal US$ 16 million (€ 12 million) that were intended for charities. He has been arrested this year in Brisbane. Authorities gave statement that Mr Hohepa Morehu-Barlow (also known as Joel Barlow) managed to misappropriate this amount over three years from Queensland Health, for which he worked as a finance manager. He allegedly used the money to fund a lavish lifestyle, occasionally even passing himself off as a "Prince of Tahiti" in social circles. The local police said that this was one of the most significant fraud cases in the history of Australia.

Australian researchers estimate trends in global prevalence of diabetes

Three researchers from Baker IDI Heart & Diabetes Institute in Melbourne used studies from 91 countries to estimate national prevalences of diabetes for all 216 countries for the years 2010 and 2030. They estimated the world prevalence of diabetes among adults (aged 20–79 years) to be 6.4% in 2010, affecting 285 million adults, and that it would be expected to increase to 7.7% (and 439 million adults) by 2030. Between 2010 and 2030, they expect a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries.

China

China's influence rapidly growing in Africa

The *Wall Street Journal* reported on China expanding its economic and political ties with countries across Africa, resulting in a rapid rise in influence. They cite US officials saying how African governments find favor with China's "state-led capitalism" path of development, which gives Chinese firms an advantage over US competitors. Mr Robert D. Hormats, the US State Department's Under Secretary for Economic Affairs, said that this was "...part of a broad notion that China's economic model is successful and can be used elsewhere". China is now the continent's largest trading partner, with its trade with Africa reaching US$ 114 billion (€ 88 billion), which is up from US$ 10 billion (€ 8 billion) in 2000 and US$ 1 billion (€ 0.8 billion)in 1980, according to China's State Council. Mr Mthuli Ncube, Chief Economist at the African Development Bank Group, estimated that "...Chinese firms accounted for 40% of the corporate contracts signed last year, to 2% for US firms". While the US often sends aid money to non-governmental groups, China mostly provides aid through government entities in consultation with leaders about what their priorities are.

China raises poverty bar to US$ 1 a day, up from 32 cents

China has taken the step of raising its poverty line to the UN's recommended standard of US$ 1 (€ 0.8) a day. Before this move, the poverty line in China was set at 1196 yuan per year per resident, which was less than 32 US cents a day. For China, this means that the number of Chinese qualified as "poor" will suddenly increase by over 100 million – to about 128 million. All of those people will now become entitled to the government's poverty alleviation program. This increase reflects a change in the financial might of China and their attitudes towards the poor. Before China's rise as an economical power, its priorities in regards to the poor were restricted to adequately feeding and clothing the population. But as GDP per capita has risen (from about 858 yuan in 1985, when China started its economic reforms, to 30 000 yuan in 2010), the ability of China to support its massive population has increased. This rise in GDP, as the *China Daily* reported, means that China now has the means to broaden its welfare program beyond the basic needs. Improving the lives of its poorest citizens is now the key aim of the Chinese poverty alleviation program.

Global Fund withholds nearly US$ 100 million intended for China's AIDS fight

The Global Fund to Fight AIDS, Tuberculosis and Malaria will discontinue funding support for HIV/AIDS programs in China. The Global Fund's spokesman Jon Liden said in the Geneva that the organization would keep about US$ 95 million (€ 73 million) from the total of US$ 270 million (€ 208 million) in grant money that was originally intended for China. This move was decided after a considerable pressure from both donors and non-governmental organizations to either fully stop, or substantially reduce funding to China. Some of them quoted possible concerns over management of disbursed funds as part of the reason, while others wanted to see the increase in funding in low-income countries where AIDS is relatively much bigger problem, but which have far fewer resources to tackle it. Apparently, this Global Fund's decision was not one-sided; it was made in consultation with Chinese officials.

China vaccinates millions in western regions to contain polio outbreak

Chinese government moved to vaccinate more than 9 million people in western regions against polio amid an outbreak that left 17 paralyzed and one dead. China had been polio-free for eleven years before the new cases were reported in Xinjiang province. This outbreak exposed gaps in immunization coverage in this remote region, where access to health services is rather low. According to the WHO, the polio strain was probably introduced from Pakistan, which is bordering Xinjiang province and is also one of the four countries where polio remains endemic – along with India, Afghanistan and Nigeria.

Chinese government and The Gates Foundation to collaborate in emerging technologies research

China's Ministry of Science and Technology and The Gates Foundation signed a memorandum of understanding under which they plan to invest together in research and development of new technologies that could improve global health and agriculture. The project, worth US$ 300 million (€ 232 million), will see every dollar provided from The Gates Foundation in support to selected China-grown products and technologies matched with US$ 2 (€ 1.6) as grant money from the Chinese Ministry. The list of considered technologies will likely be dominated by research in human and animal vaccines, diagnostics for tuberculosis and other diseases, varieties of resistant rice and other crops and more productive livestock.

Europe

Measles outbreaks reported across Europe

Recent reports from the Centre of Disease Control and Prevention confirmed that the incidence of measles was on the rise in Europe. From 2003, outbreaks of measles were steadily declining within the region, and the WHO target of measles eradication in Europe by 2010 seemed realistic. However, since 2009 rates of measles outbreaks have been increasing dramatically – with 36 of the 53 European member countries reporting outbreaks and more than 30 000 cases identified in 2010 alone. This trend has continued into 2011 and by November 2011 more than 26 000 measles cases had been confirmed. This figure has increased from less than 10 000 cases per year throughout 2007–2009. The key reason behind these figures is declining demand for vaccines and increased interest in the safety of the measles vaccine. In 2011, about half of cases of measles were in children under 15 years old with at least 45% of them unvaccinated. France has reported the greatest number of cases, about half of the entire burden in Europe in 2011. Largely, the answer to meeting the new target to eradicate measles is increase vaccination rates to maintain immunisation coverage to over 95% consistently across Europe.

Drug-resistant tuberculosis rapidly spreading in Europe

The World Health Organization announced in September that "...drug-resistant forms of tuberculosis (TB) are spreading at an alarming rate in Europe". TB is currently a worldwide pandemic that kills around 1.7 million people a year. Cases of multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB) – where the infections are resistant to first-line and then second-line antibiotic treatments – are spreading fast, with about 440 000 new patients every year globally. Half of the 30 countries with the highest burden of MDR-TB are in the WHO's European region. More

than 80 000 MDR-TB new cases occur in the European region each year, which is nearly a fifth of the world's total. Officially reported cases of XDR-TB increased six-fold between 2008 and 2009, with the rates highest in Eastern Europe and Central Asia. Treatment regimes for MDR-TB and XDR-TB can stretch into two or more years, costing up to US$ 16 000 (€ 12 000) in drugs alone and up to US$ 300 000 (€ 232 000) per patient in isolation hospital care. The risk of death from straightforward TB is about 7%, but it rises to nearly 50% among patients with drug-resistant forms.

EU will discontinue aid to 19 middle-income countries from 2014

Economic crisis that grasped European continent will have consequences for the ability of the EU to aid other countries – especially given that some of them are already surpassing large EU economies. EU officials have decided that China and another 18 middle-income countries will no longer qualify to be the recipients of the European Commission's Development Cooperation instrument. Under the European Commission's new principle of "differentiation", 19 middle-income countries whose GDP is now greater than 1% of global GDP will no longer be able to receive bilateral grant aid. Instead, they will benefit from possible new forms of partnership, which are being agreed. The other 18 countries on the list include Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Kazakhstan, India, Indonesia, Iran, Malaysia, Maldives, Mexico, Panama, Peru, Thailand, Uruguay and Venezuela.

Dutch lab concerns health officials by mutating killer virus

Several high-level health officials from different countries expressed vigilance and concern after a Dutch laboratory managed to develop a mutant version of the deadly bird flu virus that is – for the first time – contagious among humans. A research team from Holland announced in September that it had created a mutant version of the H5N1 bird flu virus that could be spread among mammals. Later in the year, it has been revealed that the US government has paid scientists to try to understand how the deadly bird flu virus might mutate to become a bigger threat. Two laboratories – one in the US and one in Netherlands – apparently succeeded in understanding this. However, US federal officials then took the unprecedented step of asking the scientists who succeeded to restrain from publishing the details of their work.

Russia plans aid for HIV-troubled eastern Europe and central Asia

According to *Financial Times*, Russia plans to offer aid to fight HIV in eastern European countries and central Asia. This move, which is seen by some analysts as Russia's latest effort to restore some of its political influence among the former Soviet Union affiliates, should offer additional funding to tackle HIV in a region with the fastest continued HIV growth anywhere in the world. The infections have tripled over the past ten years and it is estimated that some 1.4 million people are now affected. Some journalists in recipient countries expressed concern that, with this welcome aid funding, Russia could also export its restrictive policies on HIV prevention methods.

India

National Rural Health Mission "a minor success"

An official review of the Indian Government's ambitious National Rural Health Mission described it as a "minor success", adding that the results have been heartening compared to past experience in public health programmes. Deployment of human resources in the health sector has improved modestly, even though huge gaps still existed before the primary health care system could be declared to be running optimally, the report concluded. The review panel recommended that if the gains from this programme were to be consolidated, a renewed commitment for at least another seven years would be essential. The report called for almost quadrupling the per capita allocation for the health sector during the 12th five-year-plan period.

India makes steady progress in infant mortality reduction

The results of the Coverage Evaluation Survey conducted by UNICEF in India showed that infant mortality rate in this large country has come down from about 58 per 1000 live births in 2005 to about 50 per 1000 in 2009. In addition, maternal mortality ratio has also come down: it stood at 254 per 100 000 live births for the 3-year rolling period

between 2004 and 2006, but it decreased to 212 per 10 000 live births between 2007 and 2009. The immunization programme is being successfully rolled out throughout most of the country. It is estimated that up to 61% of children aged between 1 and 2 years in India are now fully immunized against 6 major vaccine preventable diseases. In December this year, pentavalent vaccination will also finally begin in several Indian states.

Twenty three children allegedly contracted HIV at a hospital in India

Large sections of the India media reported in September that at least 23 children in western India were reported to have tested positive for HIV/AIDS after receiving blood transfusions at a state-run hospital in Junagadh, Gujarat. The children – all under the age of 10 years – were among around 100 children with thalassemia, who had been receiving free blood transfusions at the hospital since January 2011. The *India Today*, India's leading news magazine, reported that the hospital did not have facility for advance screening for HIV in blood. There are fears that many more children could have been infected. However, the hospital authorities have refused to accept any responsibility. They say that the patients had arranged for the blood from blood banks themselves and the hospital had only handled the transfusions. The state government has instituted an investigation.

India gets closer to Polio Eradication

It has been over 300 days since last and only confirmed case of paralysis by wild polio virus in 2011. The case occurred in the eastern state of West Bengal in January 2011. Until the last year, India was still considered one of the polio endemic countries in the world. This apparent success in polio eradication is a result of a massive immunization drive launched by the Indian government and international partner agencies, which targeted high risk areas and introduced the new bivalent oral polio vaccine. The Indian government, however, remains cautious and plans to maintain high standards of polio surveillance.

Japanese encephalitis kills hundreds in India

Japanese encephalitis (JE), a deadly viral disease caused by flavivirus and transmitted by *Culex* mosquitoes, has killed around 900 people across India, many of them children, according to data available until the end of November 2011. The state of Uttar Pradesh in northern India has been the worst hit so far, with more than 500 reported dead. The outbreak has spread to other states like Assam, West Bengal, Tamil Nadu and Haryana. The districts of Eastern Uttar Pradesh have had similar large scale JE outbreaks in the past, with the last one reported in 2005. The Indian health minister informed the Parliament that appropriate control measures – early case detection and proper case management, JE vaccination and health campaigns promoting cleanliness, sanitation and safe drinking water have been instituted.

The Americas

Latin America enjoys lowest poverty levels for 20 years

In November this year the Economic Commission for Latin America and the Caribbean (ECLAC) announced the lowest levels of poverty in Latin America for two decades. Poverty rates decreased from 48% in 1990 to 31% in 2010, which is a drop of 17 percentage points. Meanwhile, indigence rates – those living below the minimum subsistence level – dropped from 23% to 12% over the same time period. In 2011 poverty was predicted to fall one further percentage point, to 30.4%, meaning that at the end of 2011 ECLAC foresees a total of 174 million inhabitants living in Latin America in poverty. Indigence rates were set to rise by 0.5% percentage points to 12.8% in 2011, translating to 73 million inhabitants defined as living in extreme poverty or indigence. This was linked to expected increase in prices of living counteracting the forecasted increase in household income.

Mysterious epidemic of deadly kidney disease spreads across Central America

According to *BBC News*, a mysterious epidemic is affecting the population of Central America. Reportedly, it has become the second most important cause of death among men in El Salvador. In Nicaragua, it's a bigger killer of men than HIV and diabetes added together. The epidemic extends beyond those two countries and it is prevalent along the Pacific coast of Central America, across six countries. Dr Victor Penchaszadeh, a clinical epidemiologist at Columbia University in the US and consultant to the Pan-American Health Organization on chronic diseases in Latin America,

stated about this epidemic: "It is important that the chronic kidney disease (CKD) afflicting thousands of rural workers in Central America be recognized as what it is – a major epidemic with a tremendous population impact". Reportedly, El Salvador's health minister recently called on the international community for help. Up to the quarter of the farming workers in the area seems to be suffering from the disease, which eventually kills them. Interestingly, most of those affected show no signs of high blood pressure or diabetes, which are the most common causes of CKD elsewhere in the world. Currently suspected risk factors that could be causing this kidney damage are the toxic chemicals – pesticides and herbicides – that are routinely used in agriculture in Latin America, but banned in the United States, Europe and Canada. However, the overuse of painkillers and alcohol abuse can also damage kidneys, and both are also prevalent among the affected population.

United States grow increasingly concerned over biological weapons threat

Reporting on the Secretary of State Hillary Clinton's visit to Geneva, Reuters wrote that the United States are now calling for closer international cooperation to prevent terrorist groups from developing or using biological weapons. In the era of exploding advances in genomic research of many living species, including potentially deadly viruses and bacteria, and widely commercially available technologies for genome manipulation, this threat is continuously growing. Ms Clinton was reported to have concluded: "Unfortunately, the ability of terrorists and other non-state actors to develop and use these weapons is growing. Therefore this must be a renewed focus of our efforts".

Brazil's transition from aid recipient to an important aid donor

Brazil's economy has just surpassed UK's to become the 7th largest in the world. Although it is still an aid recipient, with a lot of inequity and poverty remaining to be tackled at home, Brazil is also growing a foreign aid programme of its own, which now amounts to nearly US$ 1 billion (€ 0.8 billion). However, aid itself is not the only contributor to Brazil's growing international presence. Trade between Brazil and Africa has grown from US$ 5 billion (€ 3.9 billion) in 2003 to more than US$ 20 billion (€ 15.4 billion) in 2010 – and a third of the latter figure is generated through exchange with Nigeria alone. President Luiz Inácio Lula da Silva's vision, highlighted in his bold "declaration of international relevance", saw Brazil establishing 17 embassies in Africa, while Mr da Silva visited 23 African countries himself. Mr Marco Farani, the director of the Brazilian aid agency, said for *The Guardian* that his attitude to international aid strategy is very relaxed: "We don't have a strategy", he stated proudly. He said that his preference was to respond to requests for support, rather than spending time on comprehensive strategic planning.

Cuba launches the first vaccine for treatment of advanced lung cancer

According to *Xinhua* agency, Cuban medical authorities started selling the world's first therapeutic vaccine against lung cancer. The CimaVax-EGF vaccine comes as a result of more than two decades of research into diseases related to tobacco smoking. It has been developed by researchers at the Center of Molecular Immunology (CIM) in Havana. The active ingredient is the epidermal growth factor (EGF), a protein which is considered a biomarker of uncontrolled cancer and cell proliferation. The head researcher of the project, Dr Gisela Gonzalez, said that "...the drug could turn the cancer into a manageable, chronic disease by generating antibodies against the proteins which triggered the uncontrolled cell proliferation". This immunogenic vaccine is indicated for patients with advanced lung cancer which do not show positive response to chemotherapy or radiotherapy. The vaccine cannot prevent the disease, but according to Dr Gonzalez, it "...improves significantly the status of the critically ill patients". She added that researchers at the CIM planned to use the same principle in treating other cancers, such as prostate, uterus and breast cancers.

The Bill and Melinda Gates Foundation

Bill Gates delivers long-awaited speech on the future of development finance to G20 leaders

Invited by the French President Mr Sarkozy to address the world leaders at the G20 Summit in Cannes, France, and share his views on the future of development finance, Mr Bill Gates has delivered one of the most awaited and important speeches this year. His messages were being very carefully analyzed, interpreted and debated throughout the world press, with the response to his contribution to the summit being overwhelmingly positive. Mr Jonathan Glennie, writing for *The Guardian*, summarized the three key elements of Mr Gates' address to G20, saying that Mr Gates: "...emphasised the key features of this era of development: the steps forward in terms of development indicators, relative to previous decades. He calculated that, by focusing on good news rather than calamity, he would inspire world leaders to continued action. Gates gave great examples of change, and his intention was clear – to inspire people at a time of economic gloom. In this sense, he has moved from businessman to statesman." Mr Glennie then added that Mr Gates "...underlined what he called the "paramount importance of innovation" – his calling card. Gates's support for innovation and knowledge transfer makes him a natural supporter of south-south style development co-operation, which emphasises mutual learning as much as financial transfers. His explanation of how triangular co-operation works will be one of the key things many western leaders – still mostly illiterate in the ways the south is helping itself – take from his speech". Finally, Mr Glennie concluded that Mr Gates "...noted that some countries are emerging from aid dependence, which shifts focus firmly on to revenue mobilization." Mr Glennie expressed his personal view that "...the legally binding transparency requirements for extractive industries are far more important for development than the transaction tax, that has won all the headlines", because these requirements would generate resources and greater accountability in poor countries, which is the crucial link to institutional progress.

Forbes declares Melinda Gates world's 6th most powerful woman

The most recent annual ranking of the 100 women in the world with the greatest clout and influence, which is regularly performed by the *Forbes* magazine, declared Ms Melinda Gates the 6th most powerful woman in the world. The co-founder and co-chair of the Bill & Melinda Gates Foundation has outranked Michelle Obama (ranked 8th), Lady Gaga (ranked 11th), Queen Elizabeth II (ranked 49th) and former House Speaker Nancy Pelosi (ranked 52nd).

Novartis' head of development to lead global health at The Gates Foundation

The Bill & Melinda Gates Foundation have announced that Dr Trevor Mundel has been named their president of the Global Health Program. Dr Mundel, currently working as global head of development for Novartis Pharma AG based in Basel, Switzerland, took his post in December. The move is expected to further strengthen an already strong co-operation between leading pharmaceutical companies and the world's largest philanthropic organisation. The global health at The Gates Foundation has about US$ 1.5 billion (€ 1.2 billion) annual budget and it supports the development of new drugs, vaccines and diagnostic tools.

PATH's president to lead global development at The Gates Foundation

Chris Elias, President & CEO at PATH, an international nonprofit organization, will step down from his current position and join the Bill & Melinda Gates Foundation (BMGF) as President for Global Development in February 2012. Writing for the Centre for Global Development, Ms Nandini Oomman said that first reactions from many in global health were a surprised ones, as Mr Elias was widely recognized for his contributions to global health, and much less so to the global development. However, a more detailed analysis, according to Ms Oomman, points to the conclusion that this appointment may help bridge gaps between global health and global development and integrate the two. Integrating global health delivery into global development would result in much greater impact of global health activities, while linking the discovery and development of interventions to their delivery would fill the gap in translation that frequently exists. Ms Oomman concludes that this kind of cross-disciplinary appointments is a growing trend in a multidisciplinary world of global health, and it will be expected to have positive implications in integrating the field.

The Gates Foundation to award US$ 35 million for innovative ideas in family health

The Bill & Melinda Gates Foundation announced that it will invest US$ 35 million (€ 27 million) in grants to "...expand the pipeline of groundbreaking ideas that can help women and children live more prosperous and healthy lives". The funding was announced at the annual Grand Challenges Meeting in Delhi, India. It will fund two new Grand Challenges in Global Health grant programs through supporting research into innovative solutions for family health. Mr Chris Wilson, director of Global Health Discovery at the foundation, commented that "...there is a vital need for new and creative ideas to help mothers and children in the world's poorest countries."

The GAVI Alliance

GAVI chief on innovative finance mechanisms that led to success

Speaking for the *Global Health Magazine*, GAVI Alliance's chief, Mr Seth Berkley, discussed innovative finance mechanisms that contributed to GAVI's success. Innovative ways to deliver vaccines to children in low resource settings is at the heart of GAVI Alliance's mission which brings together governments, international organizations such as UN's bodies, vaccine manufacturers and other industry partners, civil society, large donors and philanthropists and private corporations. They share the common goal of: "...saving lives and improving health by expanding access to immunization in developing countries". As stated by Mr Berkley, "...innovative finance is designed to provide more money for health and more health for the money".

Three innovative finance products created by GAVI explained

According to *Global Health Magazine's* interview with GAVI Alliance's chief, Mr Seth Berkley, GAVI has created three innovative finance products that underlie its efficient operations. The first is "GAVI Matching Fund", designed to raise US$ 260 million (€ 201 million) for immunization by the end of 2015. Under this program, the UK Department for International Development (DFID) and the Bill & Melinda Gates Foundation have pledged about US$ 130 million (€ 100 million) combined to match contributions from corporations, foundations and other organizations, their customers, employees and business partners. The second one is "International Finance Facility for Immunisation" (IFFIm), which uses long-term payment pledges from nine donor governments (and Brazil to join soon) to create and sell "vaccine bonds" in the capital markets and ensure cash flow for the organization to purchase vaccines. It was started in 2006 as the first ever aid-financing entity to attract legally binding commitments of up to 20 years. Vaccine bonds have proven popular with all investors who are looking for both a market-based return and a socially responsible investment. The third one is "Advance Market Commitment" (AMC). It funds newer and expensive vaccines through connecting donors, the World Bank, UNICEF, WHO and the vaccine industry to provide vaccines at significantly reduced prices. Through this mechanism, companies sign a legally binding agreement to provide the vaccines at a price that would be both affordable and sustainable for developing countries in the longer term. By shaping markets, GAVI helps to reduce the prices of vaccines over time.

Praise for GAVI Alliance's innovative approach to international development aid

During the UN General Assembly in New York in September 2011, both leaders of the governments' aid programmes in USA and the UK have recognised the GAVI Alliance as "...offering "game changing" lessons in the fight against global poverty". Mr Raj Shah, who is the acting Head of USAID, and Mr Andrew Mitchell, presently UK's Secretary of State for International Development, have both highlighted GAVI as a "...model global development partnership that is significantly helping advance the Millennium Development Goals (MDGs)".

Childhood pneumonia is now a dominant target of GAVI grants

Childhood pneumonia has been the leading cause of child deaths globally for many decades, but very few policy makers were aware of this only several years ago. The work by WHO/UNICEF's Child Health Epidemiology Reference group (CHERG) drew attention to pneumonia as the leading killer of children. A number of subsequent activities, including an assessment of the burden of specific causes of

pneumonia – such as *S. pneumoniae* and *H. influenzae* type B – made it apparent that the majority of the burden could be prevented through pneumococcal and Hib vaccination. This year, in the largest-ever approval of grants for vaccines announced by the GAVI alliance, almost two-thirds of the funds would be spent on pneumonia prevention. *Development Today* reported that, of US$ 1 billion (€ 0.7 billion) intended for spending, US$ 664 million (€ 512 million) would be spent on purchasing pneumococcal vaccine for 36 million children in 12 African countries that have applied for support.

GAVI aims to introduce HPV and rubella vaccines in developing countries

According to *Reuters*, The GAVI Board announced in November that it "...will take the first steps towards the introduction of HPV and rubella vaccines in developing countries". Commenting on the decision to support HPV vaccine introduction, GAVI said that "...if negotiations to secure a sustainable price from manufacturers are successful and countries can demonstrate their ability to deliver the vaccines, up to two million women and girls in nine countries could be protected from cervical cancer by 2015". Moreover, the GAVI Alliance "...has agreed to fund the roll-out of vaccines against cervical cancer in developing countries, offering protection against a disease that kills one woman every two minutes".

The World Bank

World Development Report 2012 focuses on gender equality

Globally, women's rights are improving, both in absolute terms and relative to men. The World Bank's report says that in high-income countries there's a consensus supporting legal rights and guarantees of equality for women. In many middle and low income countries more women are literate and their education level is getting nearer that acheved by men. Women's share in the global workforce is now up to 40%, and in agricultural workforce it is even higher – 43%. Encouragingly, more than half of the university students globally are now females. Ana Revenga, co-director of the World Bank's World Development Report 2012, said upon the release of the report earlier this year that "...in today's globalized world, countries that use the skills and talents of their women will have an advantage over those that don't".

UN chief sees investing in people as the way to overcome poverty

According to *UN News*, Secretary-General Ban Ki-moon cautioned that "...progress so far in the fight against poverty risked being reversed by a failure to put people at the centre of development policies and strategies aimed at economic recovery following the global financial crisis. In the name of fiscal austerity, we cannot cut back on common-sense investments in people". Mr. Ban sent this message in a speech which marked the International Day for the Eradication of Poverty. He also noted that "...too many people have been seized by the fear of losing their jobs, their ability to feed their families and access to health care. We can meet the challenges we face – the economic crisis, climate change, rising cost of food and energy, the effects of natural disasters. We can overcome them by putting people at the centre of our work".

An independent review panel urges Global Fund to reform

According to *The Guardian*, a report from an independent high-level panel found major flaws in both the governance and oversight of the Global Fund, in spite of its good overall performance and clear accomplishments. The review was chaired by former US Health Secretary Michael Leavitt and former President of Botswana Festus Mogae. The verdict of the panel was that the Global Fund must "change or wither". The report followed a major crisis of confidence in the Fund, after the media reports at the end of 2010 implicated fraud and corruption among countries taking Global Fund money. It is now feared that this kind of conclusion could give donors the excuse to reduce or entirely discontinue their funding support to the Global Fund. This would be devastating for the efforts against HIV/AIDS, tuberculosis and malaria in low and middle income countries. In January this year, Germany had already suspended payments and there was talk of other nations also turning away.

Eurodad warns that the majority of development aid is "boomerang aid"

A study released in September in Brussels by the European Network on Debt and Development (Eurodad), a network of 58 non-governmental organisations from 19 European countries, claimed that "...development aid is ineffective mostly because it is tied to contracts worth billions of dollars awarded to firms in developed countries, in a phenomenon called boomerang aid". The study showed that more than two-thirds of all aid contracts were eventually awarded to companies in the wealthy countries. The study was deliberately released ahead of the Fourth High Level Forum in Busan, South Korea, bringing together the world's governments and stakeholders in November 2011 to consider how to make aid more effective. Organisation for Economic Cooperation and Development (OECD) estimated the total development assistance in 2009 at US$ 128 billion (€ 99 billion). Bodo Ellmers of Eurodad, who prepared the report, said that "...most people think these 128 billion were given to developing countries, but two-thirds were awarded to companies in the North, only benefiting the North's economy. Aid doesn't work as well as it could because it is not delivered in the way it should be delivered".

Eurodad's report critical of World Bank aid's procurement practices

The Eurodad study also showed that half of the contract value in World Bank-funded projects in the last decade went to firms from donor countries, with the share increasing with the size of the contract. In 2008, 67%of all World Bank-financed contracts went to firms from just 10 countries as "...a consequence of World Bank procurement practices". The study explains that most recipient countries are pressured to allow transnational companies to bid for contracts. Aid is given if the market opens up to international competition, benefiting western companies. Eurodad calls for "smart procurement" and preferential access for local or regional companies to be awarded aid contracts. Smart procurement also means "...imposing conditions on contractors that ensures that aid contributes to sustainable development".

United Nations (UN)

Donors provided nearly US$ 375 million to UN's emergency relief fund

According to the *UN News*, donors pledged nearly US$ 375 million (€ 289 million) to the United Nations emergency relief fund. This money is meant to ensure that humanitarian workers can quickly begin saving lives whenever a humanitarian crisis strikes anywhere in the world. The Central Emergency Response Fund (CERF) has disbursed more than US$ 2 billion (€ 1.5 billion) in assistance to different stricken areas since it was launched in the year 2006, making it the world's largest source of humanitarian funding.

UN calls for better land governance to fight corruption and "land grabs"

Countries must increase governance and transparency in land use to fight corruption, the United Nations' Food Agency said in a report following the UN's talks on land governance in Rome. The joint working paper by the UN's Food and Agriculture Organisation (FAO) and global graft watchdog Transparency International found corruption in the agriculture sector varies from small fraud to high-level abuses of government power. Governments should expect speculation and monitor concentration of ownership when land rights are transferred to investors to "develop" farmland. A UN special rapporteur on the right to food Olivier De Schutter spoke for *The Guardian* earlier this year: "We must escape the mental cage that sees large-scale investments as the only way to develop agriculture and to ensure stability of supply for buyers". The recent surge in food prices has prompted both investors and governments to focus on agriculture after decades of neglect, which eventually brought the attention on land deals in developing countries. A recent report by Oxfam identified 227 hectares of land – an area the size of north-west Europe – as having being reportedly sold, leased or licensed, largely in Africa and mostly to international investors in thousands of secretive deals since 2001 – i.e., considerably more than the World Bank's estimate of 56 hectares.

UN Population Fund warns that high fertility impedes economic development

The UN Population Fund (UNPF) has warned that continued high fertility in sub-Saharan Africa and southern Asia is impeding economic development and perpetuating pov-

erty in those regions. With an estimated 215 million women seeking family planning each year, but unable to gain access to it, family planning would need to be considered a priority among the local policy-makers. In its annual state of world population report, the UNPF called for health and education programs to improve this situation and enhance the development of those regions. The report was issued ahead of the human population' predicted growth to 7 billion at the end of October this year.

UN population chief says family planning opportunities missed because of HIV/AIDS focus

The Guardian reported on the interview recently given by Babatunde Osotimehin, the executive director of the UN Population Fund, related to the release of UNPF's state of world population report. Mr Osotimehin said that the international community may have "made a mistake" with the intensity of its focus on the global HIV-AIDS epidemic. Because of this effort, the ground was lost on family planning issues as a result. He added that "...efforts to expand family planning services in the developing world stalled for a decade, while global health organizations turned their energies to fighting HIV/AIDS".

Slow start to global movement against non-communicable diseases

Globe and Mail, Centre for Global Development, the World Health Organization's Press Office and many others have been following and reporting from a two-day United Nations summit on the prevention and control of non-communicable diseases (NCD). The very first gathering of such kind took place in New York in September – and according to *Globe and Mail*, it ended "...with a whimper rather than a bang". The heads of state and government leaders, senior ministers and experts who attended the meeting, all took some very modest steps to get the movement started – but according to the observers, far too few (and too small) were taken to address the urgency and magnitude of the challenge the world now confronts. The main risk factors for NCDs today are unhealthy diet, physical inactivity, tobacco use and alcohol abuse. Interventions against them could counter the NCD pandemics for a relatively modest price in comparison to the expected benefits. However, the attendees of the New York summit did not seem interested in this bargain, all of them withstanding an intense fiscal consolidation mode under the current economic climate. Ms Glassman from the Centre for Global Development suggests that "... the main outcome ... is homework for the WHO, ... (now) assigned to lead the global response to NCD, develop a monitoring and evaluation framework, provide technical assistance and track progress towards global targets – (which is) yet another unfunded mandate while WHO is in the midst of a major reform precipitated by funding cuts itself".

UN-AIDS

Three US presidents mark World AIDS Day amidst funding crisis

Thirty years after AIDS surfaced, US president, Mr Barack Obama, declared "the beginning of the end" of the disease, which is primarily due to dramatic positive results achieved by antiretroviral drugs. Mr Obama was joined on World Aids Day by two of his predecessors who also contributed to the progress – Mr Bill Clinton and Mr George W. Bush. However, this declaration came in parallel with the decision by the Global Fund to Fight AIDS, TB and Malaria to call off its latest funding round, as countries around the world are slashing their aid budgets amid global financial strife.

HIV/AIDS: Delayed Global Fund money a sign of economic times

IRIN reported that The Global Fund to Fight AIDS, TB and Malaria "...has more than halved the estimated amount of money available in its next round of funding, the disbursement of which has been delayed until 2013, due to the world economic crisis". The delay in Round 11 funding was announced at the Fund's latest board meeting in September, pushing the application deadline back to at least March 2012. The size of the available support has also decreased – to US$ 800 million (€ 617 million), which is less than a half of the US$ 1.5 billion (€ 1.6 billion) projected for the round as of mid-2011, according to Mr Christoph Benn, director of the Fund's external relations and partnerships.

UNAIDS chief endorses financial transaction tax as a way to bridge funding gap

Reuters reported recently that the Head of UNAIDS, Mr Michael Sidibe, has warned of a setback in the fight against HIV/AIDS following the funding crunch of the Global Fund. Mr Sidibe "...called for a financial transaction tax and other

taxes to finance the ongoing AIDS response instead". A linked article in the leading scientific journal *Nature* warned that donor cutbacks are threatening gains in HIV treatment. Meanwhile, UNAIDS reported the highest number of HIV infections ever in Middle East and North Africa in the year 2010, but called recent progress "promising".

A developing country-based alliance to develop child-friendly AIDS drugs

The Drugs for Neglected Diseases Initiative (DNDi), an international non-profit drug research and development organization and scientific alliance in which developing countries have the key role, has embarked on producing paediatric antiretroviral (ARV) drugs. This is a welcome initiative because this area is of little interest to large pharmaceutical companies, given that mother-to-child transmission of HIV has practically been eliminated in the industrialised world.

Global campaign launched against Abbott over monopoly on a key AIDS drug

The Guardian reported that multinational drug company Abbott is targeted by health campaigners in several countries. They are trying to break its monopoly on AIDS drug Kaletra (also known as Aluvia). This is a combination of two drugs, lopinavir and ritonavir, the latter partly developed with funding from the US government, as the campaigners point out. It is becoming increasingly important in the developing world, as the resistance to first-line drugs grows, but it is under patent to Abbott and disproportionately expensive. Basic AIDS drugs prices have been reduced from US$ 10 000 (€ 7700) per patient per year to about US$ 100 (€ 77) through generic competition, but Abbott did not allow very cheap generic copies to be made. Abbott charges the poorest countries in the world US$ 400 (€ 309), while middle-income developing countries have to pay between US$ 1000 (€ 770) and US$ 4000 (€ 3090). Public Citizen in the USA is leading the charge, but campaigners in Brazil, India, Vietnam, Indonesia, Colombia, Thailand, the Netherlands and elsewhere are all taking action – mostly by challenging Abbott's monopoly in their own legal systems.

UNICEF

UNICEF chief urges action over Sahel food crisis

Just ahead of Christmas, the Head of the United Nations Children's Fund (UNICEF) Mr Anthony Lake urged international action to prevent one million children in the Sahel region of West and Central Africa from becoming severely malnourished. He said that "...the region is vast, the challenge is great and the window is closing", and added "...to prevent a wide-scale emergency in the Sahel, UNICEF and our partners in this effort must begin at once to fill the pipeline with life-sustaining supplies to the region before it is too late". Malnutrition among children is already prevalent in the Sahel region, and the urgency is prompted by the 'lean season', when food usually runs out due to inadequate rain or poor harvests. This period can start as early as March. Mr Lake added that "...specially developed ready-to-use therapeutic foods are the best way to treat severe acute malnutrition among children under five so they have a chance to survive and recover", he added, concluding that "...the children in the Sahel are not mere statistics by which we may measure the magnitude of a potential humanitarian disaster. They are individual girls and boys, and each has the right to survive, to thrive and to contribute to their societies. We must not fail them". UNICEF appealed for nearly US$ 66 million (€ 51 million) to respond to the crisis.

UNICEF and WHO work together to prevent further mortality in the Horn of Africa

Since July this year, when famine was declared in parts of southern Somalia, UNICEF and its partners have been working hard to prevent a second, potentially more devastating wave of deaths from disease, within a context of ongoing conflicts in the region. In Mogadishu, a UNICEF and WHO-supported measles vaccination campaign began in November for 750 000 children who are 6 months to 15 years old. It comes after further 1 million children have already been vaccinated against measles in Somalia during the months after the famine struck parts of the country.

An innovative partnership between Pampers and UNICEF on track to reduce neonatal tetanus

An innovative partnership between UNICEF and Procter & Gamble's largest brand, "Pampers", has proven a real success in a fight against neonatal tetanus – a disease that is estimated to kill a baby or a mother somewhere in the world every 10 minutes. In 2008, Procter & Gamble vowed to contribute a portion of the revenue from each pack of Pampers during the fourth quarter toward a vaccine against neonatal tetanus. This started as a small pilot program in Western Europe, but since then enthusiasm from the consumers has been so strong, and the financial support to this initiative so substantial, that the disease may be eliminated by 2015. Although Pampers became one of UNICEF's largest corporate donors over the past few years, the campaign has in fact delivered year-on-year growth for Pampers sales – even in its toughest markets. This success is a new model for "cause-related marketing".

UNICEF dismiss concerns over polio outbreak in Madagascar

According to *BBC*, the United Nation children's fund (UNICEF) has denied that there has been a polio outbreak in Madagascar. UNICEF said that the mistaken concern over an outbreak of wild poliovirus came after its office in Madagascar had issued a statement that vaccine-derived poliovirus had been detected in three health children amid an immunization campaign. This in no way implied a new outbreak of polio. In fact, the last case of polio was detected on Madagascar in 1997. According to UNICEF, "...the release may have led to a misunderstanding that there is an outbreak of wild poliovirus in Madagascar".

UNICEF launches website on global polio immunization

UNICEF announced this fall that it has launched a new website – PolioInfo – "...to support and strengthen communication efforts in all the polio priority countries". The new website should make this critical social data easier to access. The website is linked to the official website of the "Global Polio Eradication Initiative" (GPEI), which focuses on the epidemiological and logistical aspects of polio eradication. UNICEF concluded that "...the two websites will work in harmony to provide a complete array of information to experts and community members".

World Health Organization (WHO)

Margaret Chan proposes "WHO priority setting" to guide the reforms

WHO's Executive Board met in October to review progress made on the reforms that were proposed earlier this year. One of the key documents presented to the Executive Board was a report on plans for priority-setting amongst the WHO's 213 projects which are currently run by its 8 divisions and 15 regional and special offices. In an era of serious resource shortage at the organization and its decreasing importance in the global health arena, a profound reform based on transparent priority setting process and reliance on comparative advantages seems like a good plan, at least in principle. The WHO's strategy document listed five "core areas" of work: (i) health development; (ii) health security; (iii) health systems; (iv) evidence; and (v) convening. The document implies that they are what WHO "does best", and they "...distinguish WHO from organizations whose prime function is to manage and disburse loans and grants as their main lines of business", and "...from institutions that develop knowledge without necessarily being responsible for its application".

WHO define "flagships that reflect global concerns" within their five priority areas

Within the five core areas that WHO proposed to prioritize through their "priority setting", as explained in the previous news item, they went further and defined "flagships... that reflect global concerns". These should be more specific areas of focus within the main priority areas. They were listed as follows: (i) communicable and non-communicable disease; (ii) health systems; (iii) equitable access; (iv) support to country achievement of MDG.

Analysts point to lack of transparency in WHO's new priority setting

A number of reporters, analysts and commentators were quick to point to an apparent lack of transparency in WHO's newly proposed "priority setting". Amanda Glassman from the Centre for Global Development questioned the transparency of this process and the choices that were being made. There seemed to be no justification in the document why are these "flagships" chosen and how exactly are, e.g., infectious diseases, health systems, supporting individual countries, or equity "reflect global concerns". Also, some questioned how prioritizing "communicable and non-communicable diseases" is "more focused", and how does it represent WHO's comparative advantage at this point in time. According to Ms Glassman, "...the report does not offer an evaluation of "what is done best" nor does it explain the mysterious, somewhat passive-aggressive reference to other organizations and its implications for WHO's comparative advantage". The reference to "...organizations whose prime function is to manage and disburse loans and grants" probably implies donor organizations such as The Global Fund, GAVI and The Gates Foundation, while a reference to "...institutions that develop knowledge without necessarily being responsible for its application" probably refers to academic institutions. However, only several years ago WHO was still the main policy developer in global health, the main distributer of the funding, and its staff was being considered to have technical supremacy in global health issues. Nowadays, they are being overshadowed in all these areas by the large new donor initiatives and the academic community. This is an entirely uncharted territory for the WHO leadership and it will be interesting to see how will they respond to these challenges and whether they are able to indeed conduct a reform that would return some of the relevance that has been lost to other organizations over the past decade. Still, most of the analysts agree that historic role of the WHO in combating communicable diseases is commendable, while their appreciation of the growing non-communicable disease burden should also be welcomed.

WHO's World Health Report for 2012 will focus on health research

The annual World Health Report, first published in 1995, is WHO's flagship publication which includes an assessment of an important global health topic and provides a world-wide assessment. In 2012 the theme will be "No Health Without Research", thus becoming the first World Health Report to highlight and analyze the impact of health research. The theme should meet WHO's core function of "stimulating the generation, translation and dissemination of valuable knowledge" and it will be assembled by Dr Tikki Pang, Director of Research Policy and Cooperation at the WHO. In a blog posted in January this year, Dr Pang had set a tone to this forthcoming report by proposing that "...ministers of health in developing countries must strive to strengthen health research in their countries by addressing several key questions, which will be the focus of the World Health Report 2012: How should research priorities be set? What human and institutional capacities are needed? How to ensure ethical and good behaviour? How to promote transparency and accountability? How should knowledge be translated into action? What is the best way to coordinate research among the many performing it, and when so many health challenges involve sectors beyond health?" The open-access journal *PLoS Medicine* will publish a special collection of papers related to this theme.

An article prompted WHO to disclose its funding sources

An article published by ForeignAffairs.com by Sonia Shah, entitled "How private companies are transforming the global public health agenda", prompted a strong response from Ms Christy Feig, the Director of Communications at the WHO. Ms Feig accused Ms Shah of making a number of erroneous statements about how the WHO is funded, primarily the one which claimed that "...voluntary contributions from private interests and others now bankroll four out of every five dollars of the WHO's budget". Ms Feig disclosed that 80% of WHO's budget is actually coming from world's governments, and that within the two-year budget period 2010–2011 precisely "...53% of the voluntary contributions came directly from governments that chose to go beyond what their annual dues require". Further 21% of voluntary contributions came from other UN bodies (such as UNICEF, UNDP and UNAIDS) and other multilateral bodies (such as the GAVI), and another 18% from large donor foundations (such as the Bill & Melinda Gates Foundation, the UN Foundation, and the Rockefeller Foundation). Of the remainder, 7% came from nongovernmental organizations, which were dominated by funding from Rotary International for work on polio eradication.

Environment

Widely anticipated, climate talks in Durban offer mild progress at best

According to *The New York Times*, the three days of the Durban climate conference yielded only modest accomplishments. There is now an agreed promise to work toward a new global treaty over the coming years. Also, the agreement has been reached over establishment of a new climate fund. UN's Secretary General Ban Ki-moon welcomed what he saw as "the climate deal". However, scientists and critics remained less than impressed with the outcome. They seem unified in their belief that whatever the accomplishments of Durban climate talks, they would surely be insufficient to curb global warming. British newspaper *The Guardian* tried to see a positive element in the outcome of the meeting, as this agreement has the legally binding character, unlike those that preceded it. The BBC declared EU and the small island states as winners of the talks, while the USA's manoeuvring space was clearly limited with the upcoming presidential elections. EU representatives argued that the key to success is Chinese adoption of green technology, such as solar panels. Many expressed concerns whether any climate fund would be giving out grants or loans, because the latter could just add to an already unmanageable debt burden in many countries.

The rules about the new climate fund still not clear

United Nation's climate summit meeting in Copenhagen two years ago, which was seen by most observers as a fiasco, eventually managed to leave the world with a rare concrete outcome: a pledge, that could be worth up to US$ 100 billion (€77 billion) each year, to assist developing countries to make transition to cleaner energy systems. At the time, Kumi Naidoo, executive director of Greenpeace, has said that the pledge showed that high-income countries were finally taking responsibility for helping low and middle income countries, which contributed very little themselves to climate change. Still, the agreement lacked practical details of where the money should come from and how should it operate to meet its targets. This year, a so-called "Transitional Committee", which comprises 25 delegates from low and middle income countries and 15 delegates from high-income countries, met four times to try to engineer a fund that should distribute up to US$100 billion (€ 77 billion) annually from the year 2020. Although the committee completed the draft in October, ahead of Durban summit, Saudi Arabia and the United States refused to approve it. Saudi Arabia has been accused for years by environmentalist groups of obstructing climate talks, while the US administration is under intense pressure to limit financing for UN's climate protection initiatives. The draft was allegedly proposing to give developing countries "direct access" to funds, limiting the role of the World Bank, which is distrusted by many leaders in poor countries; but also to provide donor nations with assurances of "payment for verified results", potentially allowing them to halt the investments.

WHO releases global survey of the best and worst cities for air pollution

The World Health Organization released the results of its global survey of the best and worst cities in the world in terms of outdoor air pollution levels. The list relied on country-reported data over the past several years. It was based on the measurement of the levels of airborne particles that are smaller than 10 micrometers ("so-called PM10s"). The list included almost 1100 cities from all over the world. Apparently, cities in Iran, India, Pakistan and the capital of Mongolia ranked among the worst in the world for air pollution. The cities in the United States and Canada are generally among the best. In this first global survey, only 11 of 91 countries met WHO standards on air quality.

Climate change alone cannot explain increasing cholera outbreaks

In summer of 2011, *New York Times* reported that cholera outbreaks seem to be on the increase. However, it quoted a new study from the Tufts University researchers, published in *The American Journal of Tropical Medicine and Hygiene*. The study has found that those outbreaks cannot be explained by global warming alone, and that a much more important factor may be the cycle of droughts and floods along big rivers.

UN tested warning system for tsunami in North Atlantic and Mediterranean region

A release from the UN said that United Nations-backed North Atlantic and Mediterranean tsunami warning system has passed a first test of its communication network. Major disasters in Indonesia and Japan in recent years, which followed strong earthquakes occurring at the ocean's bottom, have revealed the horrific power of tsunamis to cause massive mortality and economic damage for human populations. The successful test will be used as a model for the establishment of other regional tsunami warning centres, which should prevent cost on human lives.

Demography

World population reaches 7 billion at the end of 2011

It took only 12 years for human population to increase by another billion. According to "The State of World Population 2011", a report released the UN Population Fund, the number of living humans will reach 7 billion at the end of October 2011. This comes as a continuation of positive demographic trends since the World War II, during which average life expectancy rose from about 48 years (in the early 1950s) to 68 years (in 2010). It is projected that 90% of future population growth will occur in the least developed countries, which will lead to intensified competing for very restricted resources in those countries, poverty and reduced access to health services. The International Conference on Family Planning will be held at the end of 2011 in Dakar, Senegal. It is expected to bring together high-level leaders from Africa and Europe, world-class researchers, and advocates. They will discuss how to access family planning, especially for 215 million women who want to avoid or delay pregnancy, but do not have access to contraception or cannot use it for different reasons.

An economic exodus from Europe has surely started

Only years ago, the European Union was still considered a premium global sanctuary for all those trying to escape poverty, war and injustice in many other parts of the world. But the recent figures are beginning to show the unthinkable: a growing number of Europeans are leaving the continent and heading south – to Australia and South America. It seems that tens of thousands of Portuguese, Greek and Irish people have already left their homelands this year, with the same about to happen, or already happening, in Spain and Italy. The most surprising are the new migration routes – from Portugal to Angola, Ireland to Australia, Spain to Argentina. This year alone, about 2 500 Greek citizens have moved to Australia, but further 40 000 have also "expressed interest" in moving. In Ireland, things are even more dramatic – up to 50 000 people will leave this year, mostly for Australia and the USA. But perhaps most surprisingly, at least 10 000 people have left Portugal, which has life expectancy of about 79 years, for oil-rich Angola, where people live 30 years shorter on the average. Up to 100 000 Portuguese citizens now live in Angola, which is double the number in 2005. Brazilian government also reported that the number of foreigners legally living in Brazil rose from about 1 million a year ago to 1.5 million at the end of 2011, with the number of Portuguese alone rising from about 275 000 to about 325 000 within a year.

A report issued by the UN tells member states to legalize abortion

The Guardian wrote recently about a "hard-hitting report from the UN special rapporteur on health as a human right", who said that "...all states must provide safe abortion and contraception for women". However, there are member states of the UN general assembly that still prosecute women seeking abortion. This report told them very directly that they are infringing woman's human rights. Mr Arnand Grover stated in his report that "...all states should provide safe and legal abortion services for woman – as well as contraception". In countries that harbor up to 25% of the world's total population, however, it is a criminal offence for a woman to end her pregnancy, unless she had been raped, the pregnancy had been a consequence of an incestuous intercourse, or where her life was at risk. Mr Grover based his report on a rational analysis of the impact of restrictive laws on women's human rights. He also argued that the member states are wrong to prosecute women for illegal drug use or drinking during pregnancy, because "...criminalisation only succeeds in driving women away from the help they need".

Get sterilized and drive away in a Nano car

Get sterilized and drive away in a Nano car! Nano is the low cost (US$ 2700, € 2000) car launched by Tata Motors few years ago. The idea piloted by the health authorities in Rajasthan's Jhunjhunu district in India to check population growth has been adopted by other districts. Apart from the bumper prize, this limited period offer also included motorcycles, TV sets and mixer-grinders to encourage sterilization in the district. The scheme has caught the imagination of the local population and the number of persons opting for sterilization has grown five-fold compared to the previous year. Rajasthan witnessed a substantial drop in those opting for sterilization in the last decade, but now the authorities in the district are upbeat that they will once again be able to reduce the population growth rate.

Third child could now land you in prison in Kerala

This will become a reality if the Kerala Women's Code Bill 2011, which is presently being considered by the state government, is implemented. The bill recommends that a fine

of INR 10 000 (US$ 180, € 145), which could be exchanged for three months of imprisonment, is a deserving punishment to any expectant father of a third child in this Indian state. The recommendation is part of the measures intended to encourage population planning for well-being and children's development. Those parents who violate the norms would also be regarded as "legally disqualified persons". The bill also proposes an incentive for women who marry after the age of 19 and have their first child after they turn 20 years.

Economy

High-income countries worried over debts, but poverty keeps shrinking world-wide

As the media in industrialized countries spent much of the year covering Europe's roller-coaster efforts to save the common currency and assist the struggling members – resulting in unexpected withdrawals of Greek and Italian Prime Ministers George Papandreou and Silvio Berlusconi in the process – in the rest of the world the year has not been that concerning in terms of economy. All indicators are now showing that poverty could be shrinking globally. Eleven years ago, the United Nations challenged the world to halve extreme poverty by 2015 as one of the Millennium Development Goals. At this point in time, it is beginning to seem that developing nations may reach that goal. The World Bank's recent estimates projected that the low and middle income economies have, in fact, already reached 80% of that target. The number of people living on less than US$ 1.25 (€ 1) a day is projected to fall to 883 million in 2015, compared with 1.4 billion in 2005 and 1.8 billion in 1990, according World Bank statistics – a decrease in absolute terms which happens against the background of the growing world's population. The outlook for developing countries to reduce hunger, enrol children in primary school, and reach a number of related UN-set benchmarks seems similarly good.

Critics of G20 summit in Cannes focus on failure to regulate irresponsible lenders

A number of advocacy groups issued a mixed bag of critical and partially praising statements following the most recent G20 summit in Cannes, France. The group ONE, represented by Michael Elliott, its president and chief executive, highlighted the 75 minutes spent on talks about innovative finance for development (the "Robin Hood" or Tobin tax) as the greatest success, along with the speech from Bill Gates and the resulting fact that development has now become a part of the G20's agenda. The UN's World Food Programme, was "pleased by the G20's decision to exempt food aid from export restrictions and extra taxation", because "...the move would ensure food assistance continues to reach people affected by hunger as a result of high prices and humanitarian crises", as WFP's executive director Josette Sheeran told *The Guardian*. Some of the most critical tones came from the Jubilee Debt Campaign, which called for debt cancellation rather than loans to bail out private creditors. Tim Jones, policy officer at Jubilee, said for *The Guardian*: "It is incredible that the in the midst of another global debt crisis, the most powerful countries are still failing to regulate irresponsible lenders. An orderly system is needed to cancel unjust debts, neutral of both creditors and debtors. Yet the G20 seem happy to continue with the debt debacle currently being played out in Europe, as has been seen across the world for the last 30 years. The continuing history of debt crises – from Africa, Latin America, East Asia and now Europe – is that loans to bail out private creditors and enforced austerity do not work. Instead, reckless lenders need to be made responsible for their actions and debts cancelled. Global rules are needed to enable this to happen".

Europe's debt crisis could affect global vaccination funding

The International Finance Facility for Immunisation (IFFIm) has been set up to rapidly accelerate the availability and predictability of funding available for global immunization efforts. The resources raised by IFFIm fund the GAVI Alliance, a public-private partnership that provides funds to purchase and deliver life-saving vaccines and strengthen health services in low-income countries that could not achieve this themselves. The role of IFFIm in this process is to use pledges from donor governments at the GAVI fundraising meetings to sell bonds in the capital markets. The sales of those government bonds then generate instant cash required for GAVI programmes. Now, after Standard & Poor have already put the 15 Euro-zone countries on negative credit watch, they also announced that the IFFIm's triple-"A" rating would also be downgraded, because France and the Netherlands together account for about a third of the contributions to the IFFIm expected over the next two decades. The bond sales contribute about US$ 1.5 billion

(€ 1.2 billion) each year to GAVI programmes, and if the bonds are downgraded, this would increase the overall cost of GAVI programmes – i.e. GAVI would be able to supply less vaccines with the same amount of support, at the expense of higher interest of borrowing, as a result of Standard & Poor's ratings change.

Economic improvements could be achieved through collecting the evaded tax

The Guardian's journalist Richard Murphy recently reported on the Tax Justice Network's publication of the research which he has undertaken on its behalf. Using data sourced from the World Bank, CIA World Factbook, the Heritage Foundation and World Health Organisation, he estimated tax evasion for 145 countries in the world, which cover 98% of world's GDP. His estimates indicate that about US$ 3.1 trillion (€ 2.4 trillion) is being lost each year through illegal tax evasion. That is more than 5% of their collective GDP, i.e. more than a half of the money that all those countries combined spend on healthcare. Mr Murphy makes a point that, across the world, governments pay too little attention to tax evasion, claiming that the issue is smaller than it really is. They have done so because they "mainly look at errors in the tax returns they receive, ignoring the fact that serious tax evaders are outside the system". He estimates that, had the level of tax evasion in Italy or Greece over the past decade been similar to the level in the UK, both countries would not have had nearly as much external debt as they do now. He concluded that "...if tax evasion had been taken seriously and been tackled in these countries, we would not have a crisis in the Euro-zone today".

UK urged to legally prevent vulture funds from preying on world's poorest people

According to The Guardian, the UK is being urged to help close down a legal loophole that lets "vulture funds" use courts in Jersey to claim hundreds of millions of pounds from the world's most unfortunate countries. Max Lawson, head of policy at Oxfam, said that "...the government could close this loophole tomorrow if it wanted to and stop tax havens becoming the 'go-to' destinations for vulture speculators. Vulture funds legally buy up worthless debt when countries are at war, or suffering from a natural disaster, and defaulting on their sovereign debt. Once the country has begun to stabilise, vulture funds cash in their cheap debt deeds, at massively inflated cost to the countries". In the case to be decided next month before the Jersey court, FG Hemisphere – run by vulture financier Peter Grossman – is trying to collect US$ 100 million (€ 77 million) from the DR Congo on a debt that was originally US$ 3.3 million (€ 2.5 million) and was owed to the former Yugoslav government to build power lines.

Energy

Global energy consumption undergoing very strong growth

BP oil and gas company recently released their highly respected annual Statistical Review of World Energy for 2011. Most of the report focused on the very strong growth in global energy consumption. Overall energy consumption growth was 5.6% globally, which was the highest rate since 1973. Oil prices averaged the second highest level ever, with growth rate of 3.1%. The largest oil producers in the world are now Russia (12.9%), Saudi Arabia (12.0%) and the United States (8.7% of total global oil production). Growth in natural gas was 7.4%, the largest in more than 25 years. Coal consumption increased by 7.6%, which is again the highest growth rate since 2003. Coal's share in global energy consumption rose to 29.6%, with China consuming nearly half of the world's coal (48.2%). The USA had 24.7% of total global renewable energy consumption, but China had the highest growth rate of renewable energy among large countries (increase of 74.5%). Biofuels production increased by 13.8%, and renewable energy for power generation by 15.5%, the latter led by wind power – which increased by 22.7%. Hydropower consumption grew by 5.3%, with China being the top global producer of hydropower (21% of the global total) and followed by Brazil (11.6%), Canada (10.7%), and the US (7.6%). Finally, global use of nuclear energy grew by 2%.

Nuclear power development likely to slow down after Fukushima Daiichi nuclear disaster

The tsunami that struck Japan in March 11 left many horrific consequences, but global press was quick to focus on the problems at the flooded Fukushima Daiichi nuclear plant. Although it remained somewhat unclear what the true risks were as the events were unravelling, the media coverage surely made it look like the worst nuclear crisis since Chernobyl. In the aftermath of this tragedy, intense debates flooded the press over whether nuclear power could

ever be risk-free. A number of countries decided that the potential consequences of a significant accident were just too big to accept, and they reversed their plans for investing in nuclear plants – in some cases, even shutting down existing plants. The incident will likely slow the global development of nuclear power. The Chernobyl accident had the same effect in the late 80's and early 90's.

Prices of solar panels halved in 2011

The prices of solar panels decreased rather dramatically in 2011, reaching the levels to only about 50% of the prices typically present in 2010. This is certainly good news for many consumers interested in developing a personal power source for their households. However, many manufacturers of solar panels that were based in the western countries, and were only recently seen as potentially good long-term investments, are now under intense pressure because they can hardly meet their operation costs. Some among them, like Solyndra, were forced to declare bankruptcy in 2011.

US refiners' export greater than import for the first time since 1949

This year, the United States' refiners have exported more finished products than the country imported for the first time since 1949. These products include jet fuel, heating oil and gasoline. Interestingly, this development also highlighted the energy illiteracy among some journalists who reported incorrectly: "...the US had become a net exporter of oil". This was not even remotely true, because the US is still highly dependent on its oil imports. The difference this year was that the country has been using more of that oil to make finished products, which were then exported back into global markets.

A temporary victory for environmentalist in the Keystone Pipeline deadlock

Environmentalists groups and lobbies declared a victory after the US Administration announced a delay in approving the controversial Keystone Pipeline. This pipeline was proposed to deliver oil from Canada's Athabasca oil sands to the USA. Still, this delay may not mean the abandonment of the plans and it will remain interesting to follow further developments.

Peace and Human Rights

Apparent decline of war: a short-term historic trend, or a beginning of new era?

Recently, a number of analysts and scholars began to point out that since the late 1940s annual world battle deaths have fallen by more than 90%. It seems that it is not only classical big army clashes that are in decline, but also everything from low-intensity militia conflicts to civil wars. Even terrorism seems to be becoming less frequent and deadly. "*If war is really obsolete, it would be one of the most important developments in the history of the human race*", said John Mueller, chair of national security studies at Ohio State University in Columbus and an expert in conflict trends. A similar sentiment is proposed by Joshua S Goldstein, writing for *Foreign Policy* magazine. He said that that in the past decade there have been fewer wars and fewer deaths in war than at any time in the last century, and hopes that the end of American dominance will not change that. Some of the proposed explanations are that large armies are becoming harder to raise and sustain, technological advance has increased the accuracy of munitions and reduced the amount of collateral damage, and states are finding peaceful ways of resolving their disputes rather than resorting to force. Some fear, though, that the rise of China will inevitably bring it into conflict with the United States. However, Chinese military expenditure, albeit growing fast, is still a distant second with US$ 100 billion (€ 77 billion) a year in comparison to United States' US$ 700 billion (€ 540 billion). Also, Chinese interests are closely linked with those of America, given that its economy depends on exports and that it owns a large amount of US government debt – making a possible conflict entirely counterproductive to both sides. The end of American hegemony will surely be replaced by a multipolar world, in which there will be several very strong actors who may persuade each other that treaties and agreements are a better way than wars.

Nobel Peace Prize goes to three remarkable ladies for their women's rights work

This year's Nobel Peace Prize has been awarded to three remarkable ladies: Ellen Johnson Sirleaf, Leymah Gbowee

and Tawakkul Karman, for their work in advancing women's rights and the role of women in peace-building efforts. The two are from Liberia and one is a Yemeni, and they were recognized by the Nobel committee for their "*non-violent struggle for the safety of women and for women's rights to full participation in peace-building work*". The committee added that the world "*cannot achieve democracy and lasting peace "unless women obtain the same opportunities as men to influence developments at all levels of society*". Johnson Sirleaf, a Harvard-trained economist, was elected president of Liberia in 2005 – Africa's first democratically elected female president. Leymah Gbowee is a trained social worker known for her work on peace-building, truth and reconciliation in Liberia and efforts to advance women's rights across Africa. Tawakkul Karman is a young activist and chair of Women Journalists Without Chains, who has been working to promote human rights in Yemen for years; her arrest helped kick off protests by hundreds of thousands demanding the ouster of President Ali Abdullah Saleh and the creation of a democratic government.

What will replace the fallen regimes of Northern Africa?

For the first time in decades, the possibility exists that democracy may get introduced to the Middle East. However, it is still very unsure what will replace the fallen regimes of Tunisia, Egypt, and Libya, now that they have ousted autocratic leaders. It is also unclear how will the continuing turmoil in Syria, Yemen, and Bahrain end. However, the era of autocrats – many of whom have been kept in power by a strong backing from the western powers – may indeed be ending. A wind of change has swept the Middle East and Northern Africa, with dictatorial regimes being ousted by pro-democracy protesters, who mainly sought to end tyrannical rule and institutionalized corruption. The demands of the protesters, who were up against a real military might, demanded a new political dispensation, major economic and political reforms and constitutions that will guarantee free speech, dissent, and participatory democracy.

Europe to focus on democracy and human rights in aid projects

According to *The Guardian*, the EU will soon adopt its new development policy, in which a far greater focus will be placed on democracy, human rights and governance in its aid programmes. Andris Piebalgs, the EU commissioner for development, unveiled the EU's "agenda for change" and said that human rights and democracy were "...guarantors that economic development was sustainable". Even with economic worries of its own, the EU is still the world's biggest donor of official development. Mr Piebalgs said that it will seek to promote democratic rights through "good governance and development contracts" set up between the EU and countries receiving support.

An analysis shows co-occurrence between climate cycles and civil wars

In August, *The Guardian* wrote about an analysis of 250 conflicts between 1950 and 2004. It implied that 50 of them were "triggered by El Nino", which translates to "doubling the risk of civil wars". Researchers believed that the climate phenomenon, known as El Nino, may contribute to unrest by bringing about its hot and dry conditions to tropical nations. The resulting cuts in food production are thought to lead to outbreaks of dissatisfaction, which soon focus on the flaws of regional leaders and are followed by violence. The researchers quote examples of similar cycles in countries from southern Sudan to Indonesia and Peru.

Food, Water and Sanitation

Incoming FAO chief highlights three steps to hunger reduction success

The incoming Director General of FAO, Jose Graziano da Silva, recently highlighted three elements that are required within a successful strategy to fight global hunger. He firstly highlighted the need for political commitment to eradicating hunger in the low-income settings. Secondly, he suggested involvement and partnership with FAO, WFP and IFAD. Finally, he called for absolute goals beyond the Millennium Development Goals. Talking about Brazil's experience, Mr Graziano da Silva said that whatever was invested in fight against hunger was rapidly recovered, through extraordinary returns. He stressed that the consumption cycle immediately brought back revenue in taxes and the expenditure lead to new jobs and incomes.

Millennium Development Goal on drinking water "nearly achieved"

UNICEF and the WHO released a report on the progress being made on Millennium Development Goal (MDG) of improving access to safe drinking water. In view of the experts from these two organizations and their collaborators,

this MDG is increasingly likely to be achieved – possibly even ahead of the 2015 target date. The report – entitled "Drinking Water Equity, Safety and Sustainability" – reported that between 1990 and 2008 the proportion of the world's population with access to improved drinking water sources has been increasing from the initial 77% to recent 87%. The MDG target was to halve the proportion of people without sustainable access to safe drinking water, from the 23% down to 12%. We should expect that over the next couple of years this goal will be successfully reached.

Several food crises looming in Africa, Sahel tops the urgency list

Several food crises are looming in Africa: in Zimbabwe, the Sahel and the Horn of Africa. The situation in Somalia could reportedly worsen if the ban imposed by Al-Shabaab insurgents on 16 aid agencies does not get reversed. And in Kenya, which has also been affected by the drought, followed by recent floods, the crisis may also continue. Africa's Sahel region is expected to face a severe food shortage over the coming months because of rather erratic rainfall and localized dry spells. Both the EU, UNICEF and UN officials recently warned about this particular crisis. It is also estimated that about seven million people are already facing food shortages in Niger, Chad, Mali, Mauritania, Nigeria and Burkina Faso.

Current progress rate would take '200 years' to reach UN's targets on sanitation

According to *The Independent*, the UN's Millennium Development Goal to halve the number of people without access to sanitation by 2015 – also known as "target 7C" – has been failing so dramatically, that some of the world's poorest countries would require another 200 years to reach it under the current rate of progress. Nearly a billion people worldwide are presumed to live without access to clean water, while more than two and a half billion live without adequate sanitation. The latter figure includes more than a third of all humans. More than 90% of people who don't have basic access to sanitation facilities live in only about 30 countries, with the highest absolute numbers in India and China. However, the top ten recipients of water, sanitation and hygiene aid over the past decade have not been those in greatest need, but rather middle- (or even upper-middle-) income countries. Barbara Frost, chief executive of WaterAid, said for *The Independent* that "...historical and strategic interests still influence where aid is going, rather than the countries and communities where poverty and need is highest" and that "...over the past decade, least developed countries have received only 30 per cent of aid for water, sanitation and hygiene".

World Food Program awards Bill Gates for focus on small farmers in poor countries

World Food Program USA's George McGovern Leadership Award was given to Mr Bill Gates, co-chair of the Bill and Melinda Gates Foundation, for his foundation's efforts to help small farmers in the developing world overcome hunger and poverty. Mr Gates said that the combination of famine in the Horn of Africa, rising food prices, and a growing population make it critical at this point in time to help poor farmers grow and sell more food. At the G20 Summit in Cannes, France, Mr Gates delivered a report outlining how innovations and partnerships in both health and agriculture can help increase global stability and assist the poorest countries in achieving economic growth and equality.

Science and Technology

Apple co-founder Steve Jobs died in California at the age of 56

An inspiration to many of us – an ultimate visionary, the man who managed to truly change the way we spend our time, to improve our world and to develop its most valuable company – Steve Jobs, billionaire co-founder of Apple, has died in California at the age of 56. He was a genius who managed to revolutionize personal computing, mobile telephony, and even music that we listen to. Earlier this year, he stepped down as chief executive of the Apple, which he helped set up in 1976, citing illness – he had been battling an unusual form of pancreatic cancer. Apple released a statement in which they paid tribute to their leader: "*Steve's brilliance, passion and energy were the source of countless innovations that enrich and improve all of our lives ... The world is immeasurably better because of Steve*". Mr Jobs was one of the pioneers of Silicon Valley, who did a lot to help establish this region as the global technology hub. He founded Apple with Mr Steve Wozniak, his childhood friend, and they marketed together the world's first personal computer, the Apple II. He had to leave Apple after a dramatic and uneasy boardroom battle in 1985, a move for which Mr Jobs later claimed was the best thing that could have hap-

pened to him. He went on to buy Pixar, the company which now keeps creating the biggest animated movies of our time. However, after 11 years he returned to Apple when it was being written off by rivals, and engineered possibly the most remarkable comeback in business history. Apple was briefly the most valuable company in the world earlier this year, producing US$ 65.2 billion (€ 50.3 billion) a year in revenue, compared with only US$ 7.1 billion (€ 5.4 billion) in 1997. Mr Jobs' inventions that will remain remembered include *Apple I* (1976), a computer for hobbyists and engineers; *Apple II* (1977), one of the first successful personal computers; *Lisa* (1983), the first commercial computer with a graphical user interface, with icons, windows and a cursor controlled by a mouse; *Macintosh* (1984), an improved version of *Lisa*, coupled with a laser printer; *NeXT computer* (1989), a powerful workstation computer on which the world's first web browser was created; *iMac* (1998), strikingly designed as a bubble of blue plastic that enclosed both the monitor and the computer; *iPod* (2001), the first successful digital music player with a hard drive; *iTunes store* (2003), which simplified buying digital music and became the largest music retailer in the US in 2008; *iPhone* (2007), which did for the phone experience what the Macintosh did for personal computing; and *iPad* (2010), the first successful tablet computer. To date, more than a million people from across the world have shared their memories, thoughts, and feelings about Steve Jobs on Apple's website. One thing they all have in common how they've been touched by Mr Jobs' passion and creativity.

The first report of substantial effectiveness for malaria vaccine

This year has seen the first report of substantial effectiveness for a vaccine against a parasitic disease in humans. The *New England Journal of Medicine* published an interim report of RTS,S Clinical Trials Partnership's large multicenter phase 3 trial of RTS,S/AS01 *Plasmodium falciparum* malaria vaccine. The trial involved more than 15 000 children in two age categories – 6–12 weeks and 5–17 months. The study described vaccine efficacy against *P. falciparum* malaria in the first 6000 children in the older age category with an evaluation of the first 250 cases of severe malaria from both age groups. The vaccine has been developed through a public-private partnership between GlaxoSmithKline and the Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative, supported by the Bill and Melinda Gates Foundation. The vaccine is a hybrid construct of the hepatitis B surface antigen fused with a recombinant antigen derived from part of the circumsporozoite protein, the protein coat of the sporozoite. Sporozoite is inoculated by the feeding anopheline mosquito and it invades liver cells, where it multiplies before entering blood. The vaccine is intended for use among infants and young children in sub-Saharan Africa. The interim results showed 55% reduction rate against all malaria episodes and 35% reduction of severe malaria. Although most scientists hailed this study as a massive breakthrough and a major milestone achieved in global health research, those more sceptical pointed out that it not usual practice to publish the results of trials in pieces, and there does not seem to be a clear scientific reason why this trial has been reported with less than half the efficacy results available. The RTS,S/AS01 *P. falciparum* malaria vaccine should become available in about 3 years and the World Health Organization (WHO) indicated that it could recommend it for use in some African countries as early as 2015, depending on the full phase 3 trial results which are expected in 2014.

Study shows that HIV infection can be prevented with antiretroviral therapy

HIV-AIDS pandemic started 30 years ago and resulted in 60 million infections and 30 million deaths to date. However, the introduction of potent combination antiretroviral treatment in 1996 and the public health approach to treatment in poor settings in 2002 have managed to control the epidemic. After this point, the interest turned to a n obvious question – whether antiretroviral drugs could be used to prevent infections? This led to a major success in preventing mother-to-child transmission of the virus, which now needs to be scale up to reach more HIV-infected pregnant women in poor settings. The main progress this year has been reported by the *New England Journal of Medicine*: the HIV Prevention Trials Network (HPTN) 052 study has provided definitive proof that antiretroviral treatment reduces the rate of sexual transmission of HIV-1. The international trial enrolled nearly 1800 discordant couples, and the HIV-1–positive partners were randomly assigned to receive early or delayed antiretroviral therapy (when the CD4 count dropped below 250 cells per cubic millimetre or an HIV-1–related event occurred). The study showed that antiretroviral treatment of the positive partner reduced the rate of transmission to the negative partner by more than a staggering 95% Also, immediate therapy slowed disease progression in the HIV-1–infected index patient as compared with delayed therapy, with a reduction of nearly 40% and with extrapulmonary tuberculosis dominating the clinical events and driving the between-group difference.

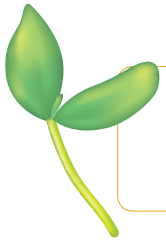
A real progress being made by seekers of another Earth

Among astronomers, the past year will certainly be remembered for the real progress being made in search for Earth-like planets in the Universe. This has been one of the main

goals of NASA's Kepler telescope in recent years, which has a capacity of planet-spotting in distant Universe – a relatively recent opportunity for astronomers. Writing for *Nature* in December this year, the scientists explained that Kepler spotted Earth sized and a Venus-sized planets in the same star system, which is about 1000 light years away from us. Both planets seem to orbit far too close to their parent star to be habitable, though. Francois Fressin, an astronomer at the Harvard-Smithsonian Center for Astrophysics in Cambridge, Massachusetts, who was the lead author of the paper, declared this discovery to be a "beginning of an era", adding that we'll soon be able to detect these kind of planets around other stars and at other distances. Kepler spots planets when they cross the face of their host stars and dim the light transmitted by the stars. This detection is very difficult when planets are as small as Earth, and researchers need to record many such transits to gain confidence in their discovery.

Antibiotic resistance predates modern antibiotic treatment by at least 30 000 years

Intuitively, many researchers assumed that bacteria began to develop antibiotic resistance exclusively as a response to antibiotic treatment which has been widely used by humans over the past several decades. However, other scientists have been suspecting for some time that bacteria have been carrying antibiotic-resistance genes since ancient times. Most antibiotics that are currently in use are developed from toxic molecules which are being produced naturally by bacteria or fungi. This has led microbiologists to suspect that genes which confer resistance to these toxic molecules should constitute a natural part of many genomes of micro-organisms. Sporadic reports claimed to have found resistance genes in bacterial samples taken from ancient sources, such as permafrost, but most studies of ancient DNA are plagues by concern that the samples may have been contaminated with modern DNA. But Gerry Wright, scientific director of the Michael G. DeGroote Institute for Infectious Disease Research, and Hendrik Poinar, McMaster University evolutionary geneticist, were able to develop methods to isolate small stretches of ancient DNA from microbes frozen in 30 000-year-old permafrost soil from the Yukon Territories. Publishing in *Nature* earlier this year, they discovered that antibiotic resistant genes existed beside genes that encoded DNA for ancient life, such as mammoths, horse and bison, as well as plants only found in that locality during the last interglacial period in the Pleistocene era.



The editors gratefully acknowledge the assistance of the following members of Edinburgh University Global Health Society to the "News" section: Tom K. Roberts, Alasdair Campbell, Robyn M. A. Watt and Andrew Morrow.

A growing concern:
How soon will India run out of water?

Rajmohan Panda

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Water resources of a country constitute one of its vital assets. India receives an average of 4000 billion cubic meters of rainfall every year, confined to the monsoon season (June through September). Unfortunately, due to lack of storage and crumbling infrastructure, only 18% can be used (1). Apart from the water available in the various rivers of the country, groundwater forms an important source of water for drinking, irrigation, industrial and other uses. Groundwater is a vital resource, with a large fraction of the population relying on the resource directly or indirectly for livelihoods. Groundwater accounts for about 50–80% of domestic water use and 45–50% of irrigation in the country (2). This heavy reliance on groundwater for both domestic water and irrigation purposes is now approaching its limit as an increasing number of aquifers reach unsustainable levels after decades of exploitation. Overall, India has around 432 cubic kilometres of annual replenishable groundwater resources. With a net annual groundwater availability of 399 cubic kilometres, the net withdrawals in 2004 amounted to 58% of the net annually available resource (3). However there are several regional and intra-state variations. According to the 2004 nationwide assessment, 29% of the groundwater blocks were in the semi-critical, critical, or overexploited categories (3).

In already large and rapidly growing segments of the economy and in many of India's most productive regions, unlimited groundwater use is no longer sustainable. A crisis situation now exists in a number of states for example In Punjab, groundwater in 75% of blocks (sub-district administration units) is overdrawn; the corresponding fraction in Rajasthan is 60% (3). The situation is deteriorating at a rapid pace. The gravity of the situation can be appreciated from the fact that the proportion of overexploited blocks nationwide has tripled from 5% to 15% between 1995 and 2004 (3). The World Bank estimate in 2005 warned that if the current trends continue, 60% of all aquifers in India will be in a critical condition within 20 years (4). In a recent study, Rodell et al. used Gravity Recovery and Climate Experiment (GRACE) satellites operated by NASA and the German Aerospace Center (DLR) to calculate the loss rate to be around 20% higher than the Indian authorities have previously estimated (5).

> Provision of clean drinking water, sanitation, and a clean environment are vital to improve the health of our people and to reduce incidence of diseases and deaths. India faces a tumultuous water future, and unless remedial measures are taken India's demand for water will exceed all its sources of supply within the next fifteen years. This short supply and scarcity will have a negative effect on public health and sanitation and regress the gains achieved.

The potential social and economic consequences of weak or nonexistent groundwater management are serious because aquifer depletion is concentrated in many of the most

populated and economically productive areas in the country. Given water's cross-cutting linkages, the implications are disturbing for the attainment of the Millennium Development Goals, for sustaining economic growth and local livelihoods, and for environmental and fiscal sustainability. Falling water tables would also be likely to affect progress in education, health, gender, child mortality, poverty, and hunger.

The exploitation of groundwater resources should be regulated so as not to exceed the recharging possibilities, as well as to ensure social equity. The detrimental consequences of over-exploitation of groundwater on the environment need urgent attention and co-operation between the central (federal) and State Governments. The Constitution lists "water supplies" under the State List while the Central Government is in "overall planning for the development of groundwater resources". Management of groundwater thus suffers from fragmentation of responsibility at both central and state levels.

The tragedy of India's water scarcity is that the crisis could have been largely avoided with better water management practices. There has been a distinct lack of attention to water legislation, water conservation, efficiency in water use, water recycling, and infrastructure. The National Groundwater Recharge Master Plan, which provides a nationwide assessment of the groundwater recharge potential, estimates that through dedicated artificial recharge structures in rural areas and rooftop water harvesting structures in urban areas a total of 36 billion cubic meters can be added to groundwater recharge, at a cost of approximately US$6 billion (€ 4.4) (6). Artificial groundwater recharge can only be a part of the solution in certain settings, but is not a holistic approach for sustainable development and management that is needed for addressing the problem of overex-

> Without a comprehensive plan being implemented to manage the water resources of the country, sustainable coverage for urban and rural habitats would not be possible. Sustainability of water availability, maintenance of supply system and water quality are major challenges for India. Conservation of groundwater, surface water, rooftop rainwater harvesting systems are some measures that should be encouraged as the means of improving water security.

Photo: Courtesy of Dr Raj Panda, personal collection

ploited aquifers storage. Thus, efforts to address excessive groundwater exploitation must also concentrate largely on the promotion of appropriate measures to manage demand, too. Dry-season crop planning, adoption of modern precision irrigation technologies, restrictions to control groundwater abstraction either voluntary (through community based management approaches) or through regulatory measures should be part of the broader solution. Groundwater management interventions should also be structured to serve the basic interests of the users, taking into account the socioeconomic realities of each particular groundwater setting.

Photo: Courtesy of Dr Akshaya Srivastav, personal collection

Funding: None.

Competing interests: The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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A global health opportunity:

The potential of multiplexed diagnostics in low-resource settings

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Diagnostic assays typically quantify a single biomarker. There are theoretical benefits to assaying multiple biomarkers simultaneously, but the studies necessary to systematically identify and validate combinations of biomarker are usually large, complicated, and expensive. Not surprisingly, there has been little effort to develop multiplexed diagnostics for use in low-resource settings. However, emerging technology may soon make simultaneous testing for multiple biomarkers feasible in formats applicable to low-resource settings. The diagnosis of serious neonatal infections is a focus of this issue of the *Journal of Global Health*, and a good example of a clinical condition that has the potential to benefit substantially from multiplexed diagnostics.

> Emerging technology may soon make simultaneous testing for multiple biomarkers feasible in formats applicable to low-resource settings. This creates an exciting opportunity to engineer new diagnostics for a variety of important global conditions.

Serious neonatal infections are responsible for nearly one million deaths per year (1). Early recognition of sepsis by a health care provider is critical for early initiation of treatment but is often hindered because newborns present with nonspecific signs and symptoms. Failure to rapidly and accurately diagnose serious neonatal infections can lead to delays in treatment and increased morbidity. Recognizing the potential to improve the diagnosis of serious neonatal infections, many researchers have evaluated biomarkers to more quickly and accurately diagnose sepsis in newborns. In this issue of the *Journal of Global Health,* we review the most promising new and emerging biomarkers for serious neonatal infections, and identify biomarkers with good diagnostic performance that seem to warrant evaluation in larger, future studies. We also looked at the few studies that examined the diagnostic potential of combination biomarkers, and found that select combinations of biomarkers showed promising performance.

There is good rationale for developing multiplexed biomarkers for the diagnosis of severe neonatal infections. Serious neonatal infection, also known as "neonatal sepsis", is not a single disease, but represents a variety of infections, due to different pathogens, which lead to complex immunologic and physiologic responses, resulting in clinical syndromes with similar features. This is reflected by the fact that hundreds of individual biomarkers have been associated with "sepsis". In this setting, focusing on a single biomarker from a single time point is potentially problematic. Using a panel of well-selected biomarkers that are not closely correlated and have different kinetics should improve the sensitivity, specificity, reproducibility, and the effective time-window of the diagnostic assay. For example, combining biomarkers that appear soon after infection, such as IL-6, with those that in-

crease later, such as CRP, could improve the time range during which the test performs well (2). Alternatively, combining biomarkers from distinct pathways in the pathogenesis of sepsis, such as mediators of inflammation with mediators of coagulation may increase the specificity of a diagnostic test for severe neonatal infections. A panel of biomarkers may also provide information beyond predicting the likelihood of sepsis. Including biomarkers known to be associated with sepsis severity could provide important information for risk stratification of infected newborns, while using biomarkers associated with different types of pathogens may guide treatment decisions before culture results are available (3). Selecting biomarkers that are inversely correlated may help control for variability in specimen concentration and processing, which could cause correlated errors in biomarker measurement. Finally, combining established biomarkers is also attractive because there has already been extensive screening of these biomarkers, and combining promising biomarkers may provide a means to efficiently leverage diagnostic performance without the need for additional biomarker discovery effort.

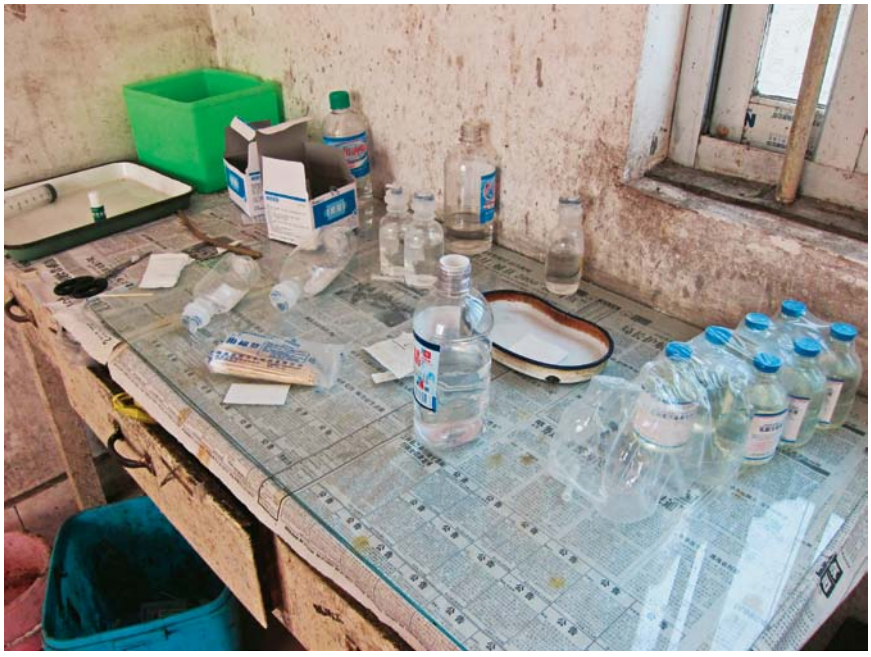


Photo: Courtesy of Dr Kit Yee Chan, personal collection

Also supporting the concept of using a combination of biomarker is the failure for any single biomarker to demonstrate sufficient sensitivity and specificity to be adopted as a gold standard for the diagnosis of neonatal sepsis. The lack of a "gold standard" is a challenge to developing diagnostics for serious neonatal infections. Sepsis is best confirmed by blood or cerebral spinal fluid culture, but culture is neither 100% sensitive nor 100% specific. Cultures can be negative when the clinical picture is felt to be consistent with sepsis, and organisms that are potentially contaminants can also grow in culture. A review of neonatal sepsis studies found that cultures were positive in only 8% to 73% of neonates treated for sepsis (4). Relying on clinical findings is problematic because even in combination with laboratory values such as CRP, clinical findings can have low sensitivity (30–60%) and specificity (60–90%) (5). A well-designed multiplexed assay may have the potential to be both more sensitive and more specific than existing tests. This would be especially attractive for low-resource settings where the burden of neonatal sepsis is high and the infrastructure necessary for microbiologic culture is often severely limited.

There have not yet been large scale efforts to develop multiplexed diagnostic tests for use in low-resource settings. However, emerging technology may soon make simultaneous testing for multiple biomarkers feasible even in low-resource settings. Recent technological improvements have fueled excitement for multiplexed diagnostic assays that can detect multiple pathogens or host markers in a single specimen (6). It is currently possible to build several test lines into a lateral flow strip, and newer technologies allow multiple independent assays to be included within a single lateral flow device (7–9). Furthermore, integrated microfluidic diagnostics have been successfully designed and engineered for use in low-resource settings. For example, see Figure 1 which shows multiplexed detection of both antigen and antibodies from a spiked blood sample. Specifically, *Salmonella typhi* IgM was detected in parallel with *Plasmodium falciparum* antigen. Both of these pathogens are common causes of fever in certain low-resource settings and bundling them together in a simple to use diagnostic should simplify and improve care in those regions.

Significant resources have been dedicated to research and development of related diagnostic technology, and it seems likely that sophisticated, multiplexed diagnostics will become increasing available in point-of-care formats. These newer diagnostics tend to utilize relatively small volumes of reagents, and by evaluating multiple biomarkers in a single device, the cost per biomarker evaluated should decrease significantly. Cost may be the most critical performance variable for diagnostic assays intended for use in low-resource settings. Most studies on novel biomarkers of sepsis evaluated the diagnostic performance of an assay without consideration of cost. A few investigators did estimate the cost per assay for the biomarker under evaluation; Ng et al measured blood serum IP-10 levels for US$ 6.55

(€ 4.9) per test using a flow cytometry bead assay (10), Cetinkaya et al evaluated serum levels of CRP or SAA for US$ 4 (€ 3) per test, and PCT levels for US$ 16 (€ 12) (11). Diagnostic tests ranging from US$ 4–16 (€ 3–12) may not represent a significant cost in resource-rich settings, but in many African countries, where the burden of neonatal sepsis is high, the average annual healthcare expenditure per capita is less than US$ 10 (€ 7.5) (12). Furthermore, the costs per assay reported above do not reflect all the costs associated with a laboratory-based assay. Most research studies are performed by skilled personnel in quality-controlled laboratories using sophisticated equipment that is also expensive to maintain. However, an ideal diagnostic test for neonatal sepsis would not rely on laboratory infrastructure, equipment, or personnel. Recent progress on developing two dimensional paper networks, allows automation of multi-step chemical processing and is being applied to antigen and IgM assays as part of the DxBox project (see **Figure 1**). Inexpensive technology offers great potential for multiplexed point-of-care diagnostic assays in resource limited settings. For example, a recent paper by Martinez et al describes an inexpensive paper cartridge used in microfluidic paper-based analytical devices (uPADS) that could be produced for less than US$ 0.01 (for paper and patterning) (8). Diagnostic technology in this price range would make multiplexed diagnostic assays feasible even in low-resource settings.

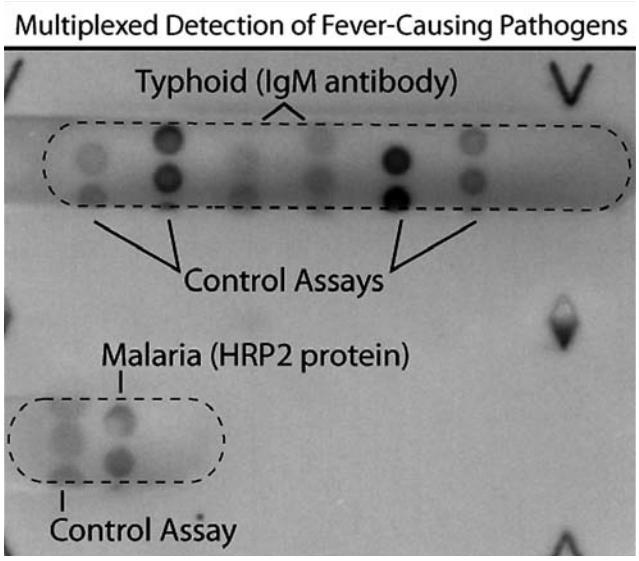
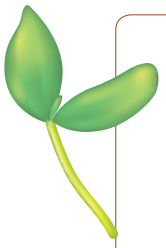


Figure 1. Multiplexed detection of both antigen and antibodies from a spiked blood sample. IgM specific to Salmonella typhi was detected in parallel with antigen specific to Plasmodium falciparum (malaria). Separate sample processing (specimen dilution and IgG removal) and two separate assay types were performed automatically on the same card. Dry reagents stored on the card were used to minimize user steps. This work was part of the DxBox, a project to perform sample-to-result identification of multiplexed fever-causing pathogens using a pneumatically actuated point-of-care device.

There are many reasons to expect multiplexed diagnostics to outperform single biomarkers. Recent technological improvements are beginning to make the cost of multiplexed point-of-care diagnostics a possibility in low-resource settings. Rigorous evaluation of combined biomarkers requires large, complicated, and expensive studies, but when feasible, future diagnostic studies should be designed to evaluate multiple biomarkers. It is especially important to advocate for these types of studies in low-resource settings, where there is less commercial interest but significant potential clinical benefit to improved diagnostics. We encourage all future studies of diagnostics for severe neonatal infections in low-resource settings to be designed with sufficient scale and statistical input to rigorously evaluate combinatorial biomarkers.

Photo: Courtesy of Dr Kit Yee Chan, personal collection



Acknowledgement: For the included image we thank Lisa Lafleur, Barry Lutz, and Paul Yager from the Department of Bioengineering at the University of Washington. Their work on the DxBox project was funded by The Bill and Melinda Gates Foundation.

Funding: Preparation of the manuscript was made possible with support from the Bill and Melinda Gates Foundation.

Authorship declaration: All authors contributed to conceptualizing and reviewing the manuscript. TW and CG drafted 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) and declare support from Bill and Melinda Gates Foundation for the submitted work. The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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Perspectives on the progress of China's 2009 – 2012 health system reform

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In July this year, China's Ministry of Health (MoH) commissioned an independent external mid-term review of progress in its current health system reform (HSR), itself designed after unprecedented input from six external agencies and the general public (1,2). In its draft report, as yet unreleased, the six-member team of eminent reviewers praises the leadership and financial commitment demonstrated by China's government in pursuing HSR, but among other things makes strong calls for harmonisation of urban and rural insurance schemes, further improvements to payment mechanisms and oversight of the quality of care, quantitative evaluations of key systems outputs and health outcomes and scientific evaluation of the benefit and cost-effectiveness of traditional Chinese medicine.

> The effectiveness and impact of China's health system reform has not yet been objectively assessed, but government is pushing ahead with impressive new initiatives involving village doctors and a computerised health management information system that should improve availability of data.

The report will be complemented by a formal internal review of the HSR commissioned by China's State Council. Previously such reports have comprised quantitative compilation of the funds allocated, facilities constructed, personnel trained and deployed, population insured and related benefits accruing, such as reduced service costs and household expenditure on health. This internal review will be informed by a "lite" version of China's five-yearly National Health Services Survey (3), focusing less on the formal Survey (next due in 2013) on health status but more on operational, funding and implementation issues related to the HSR. However, as the external review and a perusal of recent published literature makes clear, there is currently little new research upon which to quantitatively assess specific outcomes, even those directly benefiting from HSR-funded programs such as cancer screening, aged care and cataract surgery, particularly in the absence of related denominators.

China's HSR was a response to the deep inequity resulting from three decades of marketisation and de facto privatisation of the health sector (4), but despite massive injection of government funds and high uptake of insurance, out of pocket expenses for purchase of care remain witheringly high for the majority as costs rise (5), and the impact of pilot schemes and insurance is uncertain (6,7). A large reduction in the proportion of total health expenditure that is paid out-of-pocket, from a peak of 60% in 2001 to 36% in 2010 (Zhao Yuxin, China National Health Development Research Centre, personal communication), does not prove that population health needs are being met, only that government and insurance are funding a bigger proportion of services purchased. Although around a half of China's population lives in rural areas, total health expenditure and government allocations heavily favour urban areas (8). In addition, the reforms have not tackled the

health risks associated with smoking, environmental pollution, urbanisation and China's aging population – which will collectively add hugely to total health expenditure (5,9), offsetting the benefits of reform.

Notwithstanding scant objective assessment of progress, China's government is not only moving forward with HSR, but expanding its content, ambition and the resources allocated. China will shortly allocate additional finds to the 1.4 trillion renminbi (RMB) (around US$ 200 billion, € 150 billion) already provided (5), including new funds focusing on two of the five reform pillars targeting those most disadvantaged by existing inequity – primary health care delivery (10) and public health (11). It is no exaggeration to say that the government aims to establish, by 2020, a system of primary and preventive health care equivalent to that which evolved over many decades in developed nations.

Both these areas depend heavily on the front-line health workers formerly known as "barefoot doctors", whose basic education and training are very low compared to qualified doctors or even public health nurses in most developed and many developing countries. Indeed, the poor quality of care and profit motive underlying most medical treatment by village doctors in China (4) partially underlies another of the five pillars, reform of the national essential medicines scheme (12). Recognising their key role, the government is increasingly raising expectations of the role village doctors will play. A recent pronouncement by the State Council assigns to them roles previously restricted to higher levels of the health system (10).

> Reliance on implementation and majority funding of China's health reforms by sub-national authorities and the need for more attention to non-communicable disease control are major challenges for national health leaders.

Under the new guidance, village doctors will be expected to provide progressively higher quality and standardised clinical care within the constraints of China's new, zero profit approach to prescription of essential drugs (12). They will also undertake at least the ten basic public health

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activities (including aged-care, mental health, maternal and child health, vaccination and others) for which now RMB 25 (US$ 3.9, € 2.9) per capita has been allocated across rural China, up from RMB 15 (US$ 2.3, € 1.8) at the beginning of the HSR in April 2009 (11); participate in communicable disease surveillance and the national notifiable disease reporting system; administer payments through the cooperative medical (insurance) scheme (CMS) and participate in China's new computerised health management and information system (HMIS) (13), using networked computers and new software. Their payment to implement this impressive list of activities will emanate from a combination of locally-funded compensation for lost drug income, standardised fees paid by the CMS for outpatient services by diagnostic group or capitation (piloting of which is in its earliest stages in China), and subsidies taken from the RMB 25 per capita for implementation of public health services. Administration of these various income sources will be the responsibility of the county health bureau, also charged with ensuring village doctors' qualification, licensing and continuing education (10).

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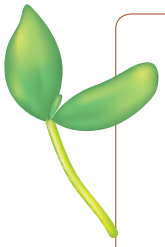
These monumental changes will bring rural health care in China into the 21st century, as befits the nation's status as a middle-income country and global economic giant. However, they connote expectations of diagnostic and therapeutic skill, public health competence, computer literacy, community participation and also administrative capacity at county level that the HSR external reviewers and people familiar with health care in rural China know are massively out of step with the status quo. In addition, given the State Council's stated expectation that supervision of village doctors will be undertaken by township and county-level professional colleagues, and that their funding will be augmented by provincial and county resources (10), this modernisation of grassroots health care in China should be viewed as a generational process.

Does that make it impossible? Only the brave would predict failure on anything so clearly supported at the highest level in modern China, but this brings attention to an old theme. In China's system of policy centralisation with financial decentralisation (8), only the highest and most politicised national priorities have a strong likelihood of being implemented at the standard desired, and indeed local adaptation of national policy guidelines is encouraged in China (14,15). In the health sector, in recent years probably only the response to the SARS crisis was pursued with the level of priority finally allocated to it by the Chinese government. Most other health policies, recommendations, strategies or guidelines including the current HSR rely heavily on being prioritised and funded by local leaders, and this cannot be assumed. As in most developing nations, population health is simply not important enough to many local leaders in China, where economic development (ie the generation, not the consumption of income) is the main objective, especially in poorer areas (5). In addition, where private sector regulation is involved the situation becomes even more uncertain; for example oversight of food safety and the pharmaceutical industry are both very much prioritised by the Ministry of Health, but rely heavily on local authorities and the participation of other sectors and interests (16,17) [witness the ongoing concerns with the dairy industry almost three years after the original melamine-tainting outcry (18,19), and recent drug-, vaccine- and food-safety scandals (20–26)]. China's HSR may be one of the highest profile and widely supported government initiatives of recent years, but the level of reliance on local funding and implementation and on other sectors suggests its success is not a given. Encouragingly, although substantive, independent assessment of the HSR and including the

perspective of citizens is lacking, there are signs of increasing consultation and attention to public opinion in many areas of public policy in China (2,27–33), making it harder for local authorities to ignore national priorities. Moreover, China's massive new online HMIS will record individualised data on health status, service uptake and payment, insurance participation and benefit, operational outputs and population-level health outcomes – all potentially in real-time (13). Failure of local support for HSR will thus become increasingly obvious as the HMIS is rolled out.

What then, of the possibility of an improved and more equitable health sector in China? In fact, like HSR in most nations, the outcome probably depends less on the MoH (which understands well the ends and is gradually devising the means to reach them), than on how other sectors and senior planners of China's socio-economic trajectory perceive the importance of population health and equity. Whilst China must certainly play catch-up with developed nations in regard to educating its health workforce, standardising quality of care, improving data systems and devising a fair system to fund and pay for services, at least it has decades of experience from other nations to draw on in these areas. Payment for care is a particular area of discussion: whilst current initiatives are directing payment to providers like hospitals and village doctors, possibly augmenting perverse incentives to provide unnecessary care, such as Caesarean section (34), an opposing perspective would direct funding toward purchasers of care, whether individuals or insurers, to encourage efficiency and quality (5,35). This is a complicated issue, but is most definitely a focus of the HSR. Much more difficult for China, and currently lacking attention, will be financing several specific health issues: non-communicable disease management and control in a population that is both rapidly aging and whose lifestyle and diet (beginning in infancy with low rates of early and exclusive breastfeeding and poor quality complementary food) increase related risk; the impact of migration and urbanisation on health outcomes; periodic crises arising from the persisting and risky mix of fierce competition and lax regulation in areas like food safety and the pharmaceutical industry; and risks arising from China's population size and density, which foments new communicable disease challenges virtually every year. In these areas, China has far fewer examples to draw on, or where solutions exist, they often cannot be reliably implemented.

It has been said that health care in China became unaffordable for the population, but that HSR might become unaffordable for the government (36). Certainly reigning in costs and improving efficiency at the same time as reducing health risks, surely an equally important component of reforming China's health sector, presents a formidable constellation of challenges for China's leaders.



Acknowledgment: The author gratefully acknowledges the helpful comments on an early draft and assistance with referencing and data from the following professional colleagues at UNICEF and WHO China and the World Bank Headquarters: Guo Sufang, Robert Scherpbier, William Bikales, Mu Yan and Hana Brixi.

Funding: None.

Ethical approval: Not required.

Competing interests: The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: No financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Balancing safety, efficacy and cost: Improving rotavirus vaccine adoption in low- and middle-income countries

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Just over a decade ago, concerns regarding vaccine-related risks led to the demise of the first rotavirus vaccine to enter the market. Licensed in the US in 1998, RotaShield was withdrawn voluntarily in 1999 by its manufacturer, Wyeth, when it was found to be associated with an increased risk of intussusception, a potentially serious and occasionally fatal intestinal obstruction estimated to occur in one case per 10 000 infants given the vaccine (1). This decision was a compelling and controversial one for global health: In seeking to avert rare but serious adverse events caused by the vaccine in the US, it nevertheless vexed efforts to address the staggering burden of diarrheal disease in developing countries. In other words, the potential benefits of a vaccine that might have prevented most of the approximately 500 000 deaths and 1.5 million hospitalizations of infants and young children in Africa and Asia each year caused by rotavirus gastroenteritis (RGE) were overshadowed by risks that some commentators have argued ought to have paled in comparison (2).

> Diarrheal disease caused by rotavirus claims approximately 500 000 lives each year, mostly in low-income countries. Many of these deaths are preventable through the use of available rotavirus vaccines. Yet, in spite of a WHO recommendation that these vaccines be adopted into all national immunization programs, only a few countries have done so.

In 2011, the rotavirus vaccine landscape has changed with two licensed vaccines recommended by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, available for adoption into national immunization programs, and several other vaccines in the development pipeline. And yet, the stark reality is that as of July 2011, only 24 countries (10 of which are low- and middle-income countries (LMICs), Sudan being the most recent) and no low-income countries had adopted rotavirus vaccines into their immunization programs (3), leaving millions of children without access to the crucial tool to prevent RGE-associated morbidity and mortality.

The barriers to uptake dotting the landscape have also changed. Safety remains an issue of some concern, particularly in light of emerging data from some post-marketing studies of the currently available rotavirus vaccines that suggest caution. However, considerations of efficacy and cost are assuming more prominence, which is appropriate as each barrier needs to be carefully assessed by decision-makers weighing benefits versus risks. Indeed, the ability to overcome other potential barriers – such as the need to enhance public perception of (and demand for) vaccines, or to stimulate the political will required to commit funding and address implementation challenges – is predicated on rotavirus vaccines demonstrating a favorable balance of benefits to risks. Numbers – efficacy data, calculations of avertable and attributable deaths, vaccine costs – are extremely useful tools, but determinations of a favorable balance (between risk and benefit; between safety, efficacy and affordability) defy simple calculation. Where numbers fail, ethical

principles can provide useful guidance. Hence, given the lives that could be saved in the very near future through improved access to rotavirus vaccines, this is an opportune time to re-examine the ethical underpinnings of assessments of benefits versus risks in the context of these vaccines.

A FINE BALANCE

The prospect of and need for more affordable vaccines that are effective in LMICs provides additional impetus for choosing this moment to reflect on our moral obligations in considering the balance of benefits and risks. Why? Because, while the best case scenario would be for the global public health armamentarium of the near future to comprise a suite of efficacious, safe and affordable rotavirus vaccines that can be rolled out as appropriate and feasible across all jurisdictions, the distinct possibility exists that new rotavirus vaccines will not hit the trifecta of being more affordable, equally or more efficacious in all settings, and equally safe or safer relative to those available today. What place, if any, is there for vaccines with equal or superior efficacy in LMICs that are more affordable, but even marginally less safe, than those currently available? Recent assertions of favourable balance of benefits to risk in rotavirus vaccination programs, while a welcome change from the dialogue 10 years ago (2), nonetheless focus on the safety and efficacy of the vaccine rather than its *effectiveness* in a real world setting, which is where cost and affordability come into the picture.

All else being equal, a lower cost – and therefore more readily accessible vaccine – would demonstrate greater effectiveness than a higher priced vaccine. But how significant does the difference in effectiveness need to be to justify the use of the more affordable vaccine, if it carries a slightly elevated risk of intussusception relative to its more expensive – and thus arguably less effective – counterpart? In answer, we can appeal to the principles of public health ethics and suggest that it may well be possible that such a marginally less perfect vaccine could, by virtue of being more affordable and thus more accessible, *promote greater good* through enhanced *effectiveness* in the face of clear *necessity* within a given context, and its use therefore ethically defensible.

SAFETY

For regulators, policy makers, global health advocates and families, the safety of rotavirus vaccines has long been a paramount concern. This is understandable, given our shared societal and moral obligation to avert preventable harm, which includes minimizing and/or mitigating harms from vaccination. The increased risk of intussusception caused by Rotashield was deemed excessively high and its withdrawal was a prudent move in the US, given its relatively low burden of diarrheal disease caused by rotavirus – some 20–60 RGE-linked deaths annually (4). However, failure to further test and deploy the vaccine in developing countries over the past decade may have cost millions of lives in those countries, in which the staggering disease burden is about 10 000 times greater than in the US (2). One need not overlook – or even downplay – the significance of the deaths that might have been caused by widespread Rotashield vaccination in high disease burden countries. However, when weighed against the potential for the vaccine to save hundreds of thousands of lives each year globally, the moral obligation to avert preventable harm should rightly have tipped the balance decidedly in favor of vaccination.

> Low uptake of vaccination is partly attributable to safety concerns that have plagued two generations of licensed rotavirus vaccines – more recently accompanied by concerns around efficacy and affordability.

The issue of intussusception persists, but is now set against increasing evidence of benefit in LMICs' settings with high disease burden. In pre-licensure studies involving more than 60 000 infants each, the currently available vaccines, RotaTeq (Merck) and RotaRix (GlaxoSmithKline), were shown to offer protection from rotavirus infection to children for the first two years of life without evidence of increased risk of intussusception among the study populations, meriting US Food and Drug Administration (FDA) licensure in 2006 and 2008, respectively (5). But post-marketing studies are still ongoing, and thus the complete data necessary to conduct a comprehensive assessment of safety among larger sample sizes across diverse populations are not yet available. In the past year, however, important data from LMICs have begun to emerge: one recent study in Jamaica found rotavirus vaccine to reduce healthcare utilization attributable to RGE without increased risk of intussusception (6). Other post-marketing studies from Australia, Brazil and Mexico showed persistent link between rotavirus vaccines and increased risk of intussusceptions (7,8). Specifically, the studies in Mexico and Brazil found vaccine-attributable intussusceptions in one in 51 000, and one in 68 000 infants, respectively, vaccinated with the monovalent rotavirus vaccine (i.e. RotaRix); at the same time, the vaccine prevented 80 000 hospitalizations and 1300 deaths otherwise caused by RGE. On the strength of these numbers, both the study authors and the editorialist in the *New England Journal of Medicine* were unequivocal in the assessments that rotavirus vaccination has a favorable ratio of benefit to risk; in fact,

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the editorial also stated that a "favourable ratio would probably also have been present with [RotaShield]" (9), demonstrating the extent to which the dialogue around benefits and risks has shifted to account for the fact that even imperfectly safe vaccines can nonetheless be responsibly used to save many lives where the need is the greatest.

It is yet unclear whether these data adequately represent the risks to populations across all LMICs, and whether health systems strengthening will still be needed before adequate post-vaccine surveillance programs can be meaningfully implemented in many LMICs where public health monitoring is often insufficient and/or ineffective (10). Nonetheless, the WHO recommends that the absence of such post-marketing surveillance at the onset should not be an obstacle to introducing rotavirus vaccines (11). In the meantime, the concept of *progressive realization*, which advocates a step-wise approach to achieving socially important goals, can be usefully applied here to help guide national and regional policy making to gradually enhance health systems' internal capacity for post-marketing surveillance. There is a lot to learn in this regard from initiatives, such as the Safety of New Vaccines (SANEVA) network developed in 2006 among 5 countries in Latin America (Argentina, the Bolivarian Republic of Venezuela, Brazil, Mexico and Panama), where one of the first foci has been to monitor cases of intussusceptions following the introduction of rotavirus vaccines in member countries (12).

What remains unclear, however, is just how imperfectly safe a vaccine could be within a given disease burden context to still have a favorable balance of benefit to risk? Here, numbers fail to provide adequate guidance: even if we were to accept that, in a country with a high disease burden, a ratio of one vaccine-linked intussusception in 51 000 vaccinated infants is favorable, and 1 in 10 000 'probably favorable', it is not obvious how to choose the appropriate bar below which it becomes probably or outright *un*favorable. Principles of public health ethics – notably including *effectiveness, necessity, and promoting the greater good* (13, 14) – can provide useful guidance.

The principle of *effectiveness* requires that if other moral considerations (e.g., *do no harm*) are to be infringed, evidence of real-world effectiveness in improving public health must be present within a certain context. At the same time, the principle of *necessity* allows for conflict across moral principles, but holds that no other method of achieving a particular 'end' would have less conflict with other moral considerations (13, 14). Because the goal of public health is to maximize the welfare of a population – *promoting the greater good* – some element of risk in a public health program (e.g., risk of intussusception) can be deemed morally acceptable if the program and its anticipated health and societal benefits are seen by decision-makers within a population – politicians, public health officials, and families alike – as satisfying the principles of *effectiveness* and *necessity*. Oral Polio Virus (OPV) mass administration, for example, has been linked to an increase in cases of acute flaccid paralysis due to vaccine-derived

We suggest using an ethics lens to examine the key operative issues that policy-makers and regulators face in low- and middle-income countries. We recommend that moral obligations in public health require due consideration of vaccine affordability alongside safety and efficacy, weighed against the potential for major public health impact, when making decisions about the introduction of rotavirus vaccine into national immunization programs.

polio virus; nonetheless, because of the health and social value of quelling the spread of polio in those few regions in which it remains endemic, OPV has remained the main vaccine of choice in mass campaigns to control polio in countries like India (15). The emphasis on *effectiveness* and *necessity* as determined within communities and/or populations highlights the importance of giving due consideration to local context, including disease burden; for example, from a public health ethics perspective, with relative disease burden seemingly overlooked in the decision to withdraw Rotashield, the assessment of risks versus benefits – based solely on numbers in one context, but not in others – was flawed, and terribly costly.

EFFICACY

Experts continue to be flummoxed by data showing that rotavirus vaccines demonstrate lesser protective rates of efficacy in LMICs as compared to 85–98% seen in high-income countries (16). This phenomenon, often termed the 'tropical barrier', is not yet fully understood. Researchers have implicated factors such as mucosal immune dysfunction brought about by repeated infections, poor nutrition (17), and higher titres of IgA and neutralizing activity in breast milk (18). Recent data have seemingly assuaged previously articulated concerns about the potential for concomitant administration of multiple oral vaccines (such as OPV and rotavirus vaccine) to contribute to the reduced efficacy (19). Efficacy may be further compromised in some LMICs' settings, like India, in which the available rotavirus vaccines do not provide protection against all the prevailing strains (20). Reduced efficacy alone, however, should not deter policy makers in LMICs from accelerating their adoption, as the potential public health benefits – lives saved and infections averted – are still highly significant. A recent analysis assuming vaccine efficacy of 50% in a national rotavirus immunization program implemented in India estimated that it would still prevent approximately 44 000 deaths, 293 000 hospitalizations, and 328 000 outpatient visits annually, which would avert US$ 20.6 million (€ 15.7 million) in medical treatment costs for the country (21).

While there is a need for continued fundamental and applied research to better understand and improve the efficacy of rotavirus vaccines in LMICs (19), it is critical to also acknowledge that the real-world *effectiveness* of the vaccines in LMICs would depend not only on efficacy, but also on a number of other factors, including access to health care.

COST

At the moment, there appears to be some consensus that the potential for rotavirus vaccines to save hundreds of thousands of children's lives outweighs their still uncertain, but potentially modest increased risk of intussusception, and variable efficacy in LMICs. However, in order for the benefits to be realized, these or other rotavirus vaccines must be affordable enough to reach those whose lives they are expected to save. It is therefore unsurprising that safety and efficacy concerns appear now to be matched by concerns about the affordability of the vaccines for LMICs (22–24).

In June 2011, GSK and Merck took a laudable step towards addressing this barrier by announcing that they would make their vaccines available to the GAVI Alliance at significantly reduced prices for use in the 72 LMICs currently eligible to receive GAVI support for rotavirus vaccines (25,26). However, even at the drastically reduced rates, the cost of vaccinating entire populations of children in many LMICs may remain very challenging, or even prohibitive. By exceeding its funding targets at its recent pledging conference (27), GAVI has proven capable of galvanizing funders' support for vaccines. Still, a successful global rollout of rotavirus vaccines will require not only the pledged support, but also much more, including the commitment of LMICs' governments to co-financing. Moreover, other authors have recently noted that the uncertainty around poor countries' capacity to sustain their access to affordable vaccines in the post-GAVI period will probably remain the largest for rotavirus vaccines (28).

Bridging the funding gap will likely depend on the introduction by innovative developing world vaccine manufacturers of new, markedly less expensive rotavirus vaccines, several of which are under development. Farthest along are candidate vaccines from Bharat biotech (Phase III) (29) and the Serum Institute of India (Phase II) (30). In a remarkable display of optimism, Bharat biotech has already committed to making its vaccine available for US$ 1 (€ 0.8) per dose, expecting licensure in India in 2014 and WHO prequalification the following year (31). LMICs' develop-

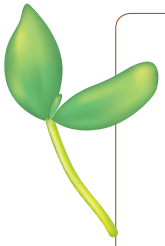
Through a careful application of the principles of effectiveness, necessity, and promotion of the greater good, we argue that there is a moral imperative to implement this life-saving public health intervention on a priority basis in parts of the world where it is needed most.

ment and manufacturing of low cost alternatives could dramatically alter the landscape – much as it did for HIV treatment through the manufacture of low cost generic antiretroviral drugs over the past decade – not least by spurring developed world manufacturers to further reduce the prices of their products. As prices fall, the accessibility of rotavirus vaccines and their potential to prevent RGE-related mortality and morbidity in LMICs will rise.

MOVING FORWARD

The rotavirus vaccine landscape is much different today than it was a decade ago. It will continue to evolve for the foreseeable future with the emergence of new data and vaccines. Efforts to mitigate risks will continue through improved post-marketing surveillance, better health systems and safer vaccines. Newer vaccines will improve on efficacy in low-resource settings by incorporating knowledge about factors predisposing enteric vaccines to the tropical barrier. Global funding agreements, advocacy and the marketplace entry of vaccines developed by innovative southern companies will bring down the cost of vaccines.

While we cannot be certain of how the safety, efficacy and cost profiles of rotavirus vaccines will change over time, it is still likely that no single vaccine will demonstrate the perfect combination of total safety, complete efficacy and sufficient affordability for use in all contexts where it is needed. Regulators and public health officials in LMICs will need to continue to assess the balance of benefits versus risks in making decisions to approve and/or adopt rotavirus vaccines in their respective jurisdictions. Because *effectiveness* is affected not only by how safe and efficacious a vaccine is, but also whether it is accessible, we contend that such assessments, normally based on safety and efficacy alone, must also include affordability. Furthermore, we suggest that this rationale should not only apply to rotavirus vaccines, but also to other vaccines targeting diseases that disproportionately impact populations in LMICs, such as pneumococcal vaccines. Neglecting to do so in the case of rotavirus vaccines would – once again – keep an effective and life-saving public health intervention from those who need it the most, and constitute a moral failure in global health.



Acknowledgments: We thank Jennifer Bell, Jocalyn Clark, Lauren Leahy and Peter A. Singer for their comments on earlier drafts of this manuscript.

Funding: This work was funded by the Bill & Melinda Gates Foundation. The funders had no role in the decision to submit this paper other than providing comments on an earlier draft.

Authorship declaration: AB and SKG conceived the article. Both collectively wrote the first draft, contributed to revisions and agreed upon the final version.

Competing interests: The authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: The authors are members of the Ethical, Social, Cultural and Commercial (ESC²) Program in Global Health at the McLaughlin-Rotman Centre for Global Health, which receives funding from the Bill & Melinda Gates Foundation, a founding partner of the GAVI Alliance. An earlier version of the manuscript was circulated to program officers of the funder, who had an opportunity to provide comments.

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journal of global health

PAPERS

Aetiology of community-acquired neonatal sepsis in low- and middle-income countries

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Background 99% of the approximate 1 million annual neonatal deaths from life-threatening invasive bacterial infections occur in developing countries, at least 50% of which are from home births or community settings. Data concerning aetiology of sepsis in these settings are necessary to inform targeted therapy and devise management guidelines. This review describes and analyses the bacterial aetiology of community-acquired neonatal sepsis in developing countries.

Methods A search of Medline, Embase, Global Health and Web of Knowledge, limited to post-1980, found 27 relevant studies. Data on aetiology were extracted, tabulated and analysed along with data on incidence, risk factors, case fatality rates and antimicrobial sensitivity.

Results The most prevalent pathogens overall were *Staphylococcus aureus* (14.9%), *Escherichia coli* (12.2%), and *Klebsiella* species (11.6%). However, variations were observed both between global regions and age-of-onset categories. *Staphylococcus aureus* and *Streptococcus pneumoniae* were most prevalent in Africa, while *Klebsiella* was highly prevalent in South-East Asia. A notably higher prevalence of Group B *Streptococcus* was present in neonates aged 7 days or less. The highest case fatality rates were recorded in South-East Asia. *Klebsiella* species showed highest antimicrobial resistance.

Conclusion Data on community-acquired neonatal sepsis in developing countries are limited. Future research should focus on areas of high disease burden with relative paucity of data. Research into maternal and neonatal vaccination strategies and improved diagnostics is also needed. All of this could contribute to the formulation of community-based care packages, the implementation of which has significant potential to lower overall neonatal mortality and hence advance progress towards the attainment of Millennium Development Goal 4.

Approximately 1 million deaths a year occurring in the neonatal period (0–28 days) are caused by infection, accounting for over 25% of global neonatal deaths and 10% of all mortality in infants under the age of 5 (1); 99% of these deaths occur in developing countries (2). Neonatal sep-

sis is classically defined as the presence of symptoms of sepsis in the neonatal period combined with bacteriological isolation of an infectious agent from blood or cerebrospinal fluid (CSF) (3). It is classified as 'early-onset' if it occurs within the first 7 days of life and as 'late-onset' if it occurs after this time. Typically, early-onset sepsis is considered maternally-acquired, usually from the maternal genital tract, and late-onset sepsis is generally regarded to originate from the care-giving environment – either a healthcare or community setting. Consequently early- and late-onset sepses are also associated with different distributions of pathogens (4).

The majority of babies in developing countries are born at home and at least a half of neonatal deaths occur in home births (5). Reasons for this include poor health system coverage or provision and limited or no access to referral facilities (6). There is significant evidence that in rural areas neonates often do not receive required healthcare and that this is associated with an increase in mortality (7). However, other reasons for the high prevalence of home births can be suggested, such as financial constraints. This is because even when health care services are available, and of respectable quality, they may still remain beyond the financial means of many (8). There are also potential sociocultural issues related to the rejection of health care services for newborns, because research has demonstrated a high prevalence of refusal of hospital referrals by their families and highlighted the need for education programmes on appropriate care seeking (9).

The predominance of home births in developing countries is not reflected in related research as this mainly provides data on neonatal sepsis in hospitals, a large percentage of which is nosocomial (10). There are several potential reasons behind the lack of aetiological data on neonatal sepsis acquired in the community, including lack of sufficient laboratory facilities in rural areas and also potentially low levels of care seeking, resulting in much unreported morbidity and mortality. This may particularly be true for the cases that occur in the areas without access to health care, or in areas with poorly developed care-seeking behaviour (4). This review is concerned specifically with the bacterial aetiology of life-threatening, community-acquired neonatal sepsis (CANS).

Pathogenesis and risk factors

Due to their immature immune systems and incompletely developed skin barriers, neonates are more susceptible to infection (11). In developing countries, the likelihood of infection is increased due to other additional risk factors. Unsafe birthing practices are common, with only 35% of births in some of the least developed countries being attended by a skilled birth attendant (12), often resulting in unhygenic practices such as delivery onto a unsterile floor, unsterile cord cutting and potentially unsafe cultural customs such as spreading dung on the newborn's umbilicus (10). Other predisposing risk factors for infection in neonates include low birth-weight, prematurity, prolonged rupture of membranes and a long delivery period (3).

Health education can also be a problem with early detection of CANS in developing countries often being low, potentially due to mothers failing to notice important symptoms and seek healthcare. The role of women in some societies is also an issue, with woman having a low social standing and a lack of autonomy resulting in delays in, or absence of, care seeking for infant's health, poorer sanitation and a decrease in access to healthcare facilities (10).

Management

Management of neonatal sepsis in a hospital setting is commonly through parenteral antibiotic therapy and supportive care, which has shown positive impacts (10). However, it is important to note that most neonates in developing countries do not receive this therapy because they do not have access to the necessary health services, or their parents do not seek care. A recent review showed a significant reduction in mortality from CANS as a result of introducing perinatal care packages including injectable antibiotics to the community (6). Research shows that the aetiology of neonatal sepsis is continually evolving, and therefore continuing updating of aetiological data is necessary to inform appropriately targeted therapy (10). A previous review of CANS showed a predominance of gram-negative organisms over gram-positive, with the main causative pathogens being *Klebsiella* species, *Escherichia coli* and *Staphylococcus aureus* (4). The focus of this review will be to provide updated data on the aetiology of CANS globally.

Prevention

In addition to efforts to improve diagnosis and treatment of CANS, efforts to prevent this life-threatening illness are also important to consider. A review of possible preventative interventions for improving neonatal health highlighted a need for universal provision of antenatal care for mothers in developing countries as a means of decreasing mortality from neonatal sepsis (13). This involves educating mothers about hygienic birth practice, promoting breast feeding and also detecting and treating important maternal risk factors for neonatal sepsis, such as asymptomatic bacteriuria (13). Another important potential way to prevent neonatal sepsis is to train and provide adequate numbers of skilled birth attendants in the community (10).

Possibly one of the most important preventative interventions after birth is early and exclusive breastfeeding. Breast milk contains important immunological factors, some of which have the potential to inhibit causative pathogens of

neonatal sepsis (11). This is a major issue, as recent research has shown that only 37% of infants younger than six months of age in developing countries are exclusively breastfed (14). Consequently, promotion of breastfeeding in community settings is the subject of an extensive World Health Organization (WHO) strategy document (15).

International responses to neonatal sepsis

Neonatal sepsis is an important issue internationally, especially with relation to the United Nations Millennium Development Goals. Without a reduction in newborn deaths, of which sepsis is a major cause, the fourth goal of reducing mortality in children under five by two-thirds cannot be achieved (2). There is therefore a need to investigate prevention, diagnosis and treatment strategies and their potential for implementation or improvement globally (8).

Founded in 1992 by the WHO and the United Nations Children's Fund (UNICEF), the Integrated Management of Childhood Illness initiative (IMCI) is an integrated approach to improving child health globally, which provides guidelines including curative and preventative elements in both healthcare and community settings. Rather than an individual disease-specific approach, IMCI has a wide and integrated strategy, aiming at addressing the varied risk factors for childhood illness (16). This approach is highly relevant in the case of neonatal sepsis as the disease has many risk factors and can be both healthcare- and community-acquired. In many settings where CANS is prevalent, high-quality diagnostic facilities are not widely available and the determination of commonly observed clinical signs provided by IMCI guidelines could be key in increasing diagnosis of neonatal sepsis and improving health outcomes (10).

Emerging antibiotic resistance is also important to consider in relation to CANS. A recent review in this area concluded that data concerning antibiotic resistance in CANS are very limited, but nevertheless highlighted potential cause for concern resulting from studies showing emerging resistance in *Klebsiella* species and *E. coli* although levels of resistance were noted to be lower than in hospital settings (17). Emerging antibiotic resistance is a major international concern (18) and the information about the aetiological spectrum of CANS and the prevalence of antibiotic resistance among major causal pathogens are important to build a broader understanding of this important public health issue.

Aims of this study

The aims of this study were to provide information on the bacterial aetiology of CANS in developing countries and to discuss the implications of the information generated for future research and international child health policy in this field. The specific objectives of this systematic literature review were to determine the bacterial aetiology of CANS in developing countries through systematic literature review, to investigate aetiological variations between global regions and different ages-of-onset and to explore potential suggestions from information presented for future policy and research.

METHODS

A review of published literature was undertaken using the electronic databases Medline, Embase, Global Health and Web of Knowledge. The search involved combinations of Medical Subject Headings (MeSH) and keywords in conjunction with a search for each individual developing country. These were defined as low- or middle-income countries from World Bank classifications (19). Search terms used for Medline and Embase are shown in **Table 1**. Terms for oth-

Table 1 Search terms for Medline/Embase

1.	Developing Countries/ or Algeria/ or Egypt/ or Libya/ or Morocco/ or Tunisia/ or Cameroon/ or Central African Republic/ or Chad/ or Congo/ or "Democratic Republic of the Congo"/ or Gabon/ or Burundi/ or Djibouti/ or Eritrea/ or Ethiopia/ or Kenya/ or Rwanda/ or Somalia/ or Sudan/ or Tanzania/ or Uganda/ or Angola/ or Botswana/ or Lesotho/ or Malawi/ or Mozambique/ or Namibia/ or South Africa/ or Swaziland/ or Zambia/ or Zimbabwe/ or Benin/ or Burkina Faso/ or Cape Verde/ or Cote d'Ivoire/ or Gambia/ or Ghana/ or Guinea/ or Guinea-Bissau/ or Liberia/ or mail/ or Mauritania/ or Niger/ or Nigeria/ or Senegal/ or Sierra Leone/ or Togo/ or "Antigua and Barbuda"/ or Cuba/ or Dominica/ or Dominican Republic/ or Grenada/ or Haiti/ or Jamaica/ or "Saint Kitts and Nevis"/ or Saint Lucia/ or "Saint Vincent and the Grenadines"/ or Belize/ or Costa Rica/ or El Salvador/ or Guatemala/ or Honduras/ or Nicaragua/ or Panama/ or Mexico/ or Argentina/ or Bolivia/ or Brazil/ or Chile/ or Colombia/ or Ecuador/ or Guyana/ or Paraguay/ or Peru/ or Suriname/ or Uruguay/ or Venezuela/ or Antarctic Regions/ or Arctic Regions/ or Kazakhstan/ or Kyrgyzstan/ or Turkmenistan/ or Uzbekistan/ or Borneo/ or Cambodia/ or East Timor/ or Indonesia/ or Laos/ or Malaysia/ or Mekong Valley/ or Myanmar/ or Philippines/ or Thailand/ or Vietnam/ or Bangladesh/ or Bhutan/ or India/ or Sikkim/ or Afghanistan/ or Iran/ or Iraq/ or Jordan/ or Lebanon/ or Syria/ or Turkey/ or Yemen/ or Nepal/ or Pakistan/ or Sri Lanka/ or China/ or Hong Kong/ or Macau/ or Tibet/ or Korea/ or "Democratic People's Republic of Korea"/ or Mongolia/ or Taiwan/ or Albania/ or Lithuania/ or Bosnia-Herzegovina/ or Bulgaria/ or "Republic of Belarus"/ or "Macedonia (republic)"/ or Moldova/ or Montenegro/ or Russia/ or Bashkiria/ or Dagestan/ or Moscow/ or Siberia/ or Serbia/ or Ukraine/ or Yugoslavia/ or Armenia/ or Azerbaijan/ or "Georgia (republic)"/ or Melanesia/ or Fiji/ or Papua New Guinea/ or Vanuatu/ or Micronesia/ or Palau/ or Polynesia/ or Samoa/ or "Independent State of Samoa"/ or Tonga/ or Comoros/ or Madagascar/ or Mauritius/ or Seychelles/ or Solomon Islands.mp. or Marshall Islands.mp. or (Sao Tome and Principe).mp. or Maldives.mp. or Tuvalu.mp. or (West Bank and Gaza).mp. or American Samoa/ or Romania/
2.	exp Infant, Newborn/ or (newborn* or neonat*).tw.
3.	exp sepsis/ or exp infection/ or (infection* or pathogen* or organism* or bacter* or etiology).tw.
4.	Limit 3 to "etiology (sensitivity)" [Limit not valid in Embase; records were retained]
5.	(neonat* adj3 sepsis).tw.
6.	2 and 4
7.	5 or 6
8.	1 and 7

er databases were slightly modified where necessary, to fit the search terms offered in the respective databases. Final searches on all databases were undertaken on 30 January 2011. Searches were supplemented by screening reference lists of selected papers and including literature discovered that corresponded with inclusion criteria.

Inclusion and exclusion criteria

Although it started with no time limits, the review was eventually restricted to literature published after 1980, to limit the number of studies and to present current aetiological data. No restrictions were used concerning publication type or language of publication. All life-threatening invasive bacterial infections (bacteraemia, pneumonia and meningitis) affecting infants of 0–90 days of age were included.Studies reporting viral or fungal infection, nosocomial infection, congenital infection or other infections such as *ophthalmia neonatorum*, malaria, tetanus or tuberculosis were excluded. All studies reporting CANS were included, along with studies where the setting or infection type reported suggested CANS. A certain number of studies were found where it was thought that CANS was indicated, however. However, the study data were deemed inconclusive to justify this assumption with a sufficient degree of certainty. These studies were included for data extraction, but not for the final data analysis. Isolated organisms from both blood and CSF were included.

Studies reporting less than 50 cases were excluded, to increase the potential to generalise from results and prevent large deviations in suggested prevalence due to small sample sizes and chance effects. Studies reporting the incidence/prevalence of only one organism were also excluded, for the same reason of likely over-estimation and the effects of chance. Review articles were also excluded, because primary data were the focus of the review. These were, however, used as helpful sources of reference.

Data extraction

Data were extracted from all selected studies and compiled in Microsoft Excel spreadsheets. An overall table of study characteristics was formed (**Supplementary Table 1**) and individual tables for each study were compiled, charting quantities of organisms isolated from blood-culture proven CANS (**Supplementary Table 2**) (20–46). This data was further split into ≤7 days of life, 7–59 days of life and 60–90 days of life based on the neonatal age at isolation of organism, henceforth described as age-of-onset (**Supplementary Table 3**). The first category corresponds to early-onset sepsis as described in the introduction. The second category corresponds to late-onset sepsis but was expanded to fit the WHO definition of a 'young infant' (7–59 days). The third category includes any data after this period up to 90 days. For several studies data were not reported in the categories described above and so it was necessary to redistribute so as to standardise for analysis. Some studies reported overlapping aetiological data for CSF and blood isolates (i.e. more than one isolate for an individual patient), in these studies it was decided to only extract data on blood isolates to avoid distortion of the results.

It was decided through the study of primary data descriptions and previous reviews not to extract data for certain organisms, including *Myma polymorpha* and *Micrococci* sp. as they were deemed to be contaminants. Although previous studies have excluded altogether data specifying infection from coagulase-negative *Staphylococci,* which are known to be common opportunistic pathogens in hospital-acquired infections, but are seen as likely to be contaminants in CANS (4,47), it was decided to extract data for these organisms but exclude them from summary tables.

Data analysis

For the purpose of analysis, data tables from studies were separated into 6 WHO global regions as illustrated below (**Figure 1**). Summary tables using the aetiological categories above were assembled for each region and relative percentages of each organism calculated (**Supplementary Table 4**). Tables for each region were then compiled, detailing only potentially pathogenic organisms so as to gain clearer insight into aetiology. Decisions on pathogenicity were based on those of previous reviews and also the information from other published literature (2,4,48). The 'other/unspecified' category for Gram-positives and Gram-negatives was removed from potential pathogen tables along with the Non-stated/Undetermined category.

Regional relative percentages for potential pathogens were calculated along with 95% confidence intervals and these were combined through meta-analysis to counteract issues with data bias and create an 'All Regions' category (**Supplementary Table 5**). Either the fixed effect model (Mantel-Haenszel method) or in cases of heterogeneity the random effect model (DerSimonian-Laird method) were used (49). Between-study heterogeneity was quantified by calculating the Q statistic with a p-value less or equal than 0.05 being the threshold (49). The meta-analysis results were unstable for several pathogens due to the small quantity of data, therefore it was decided for the purpose of analysis to use median and inter-quartile (IQ) range data from regional percentages for all potential pathogens and meta-analytical data of regional percentages for the cumulative 'Potentially pathogenic Gram-positives/negatives' columns.

As 30% of studies reported aetiological data using just numbers of positive isolates for each organism as a denominator rather than the number of patients with positive isolates for each organism, some studies reported more iso-

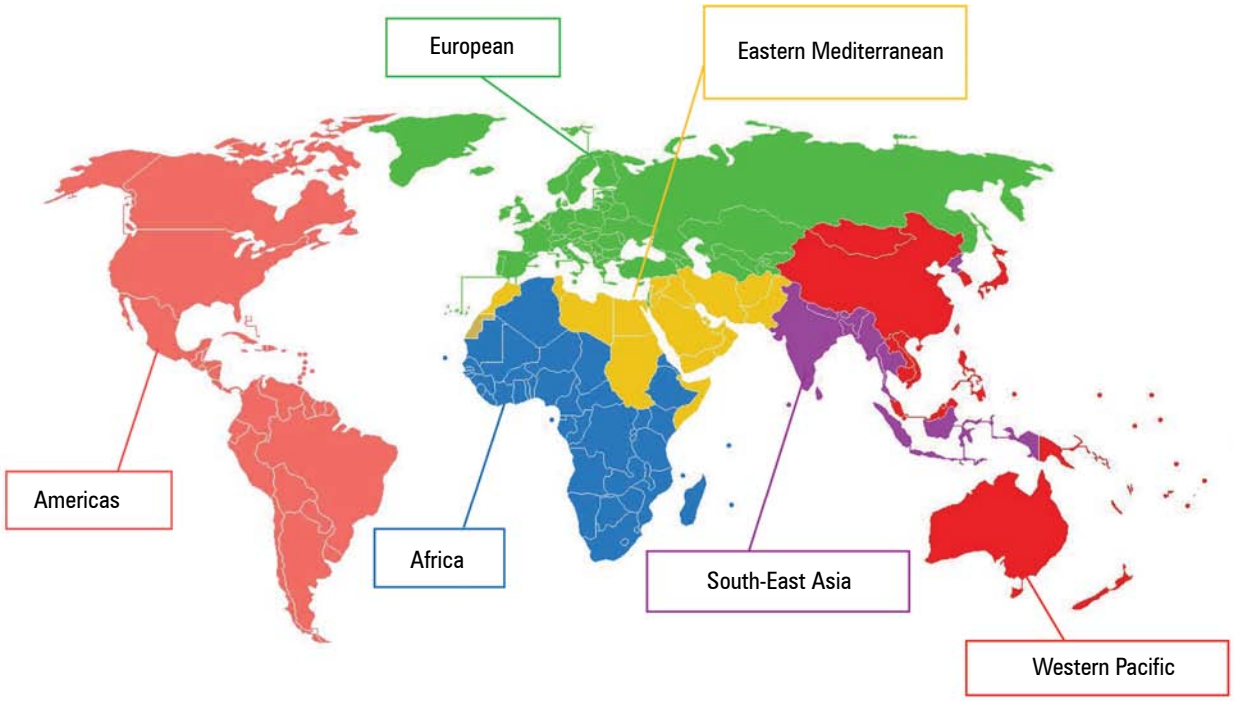


Figure 1 WHO Regions (adapted from Wikimedia Commons; http://commons.wikimedia.org/wiki/File:World_Health_Organisation_regional_offices.PNG).

lates than the number of patients in their sample. Therefore it was deemed necessary to split aetiological data into that based on patients and that based on isolates so as to determine and analyse any differences. Other data on incidence, case fatality rates, risk factors for CANS and antimicrobial susceptibility patterns were extracted where available and analysed.

Quality control

To ensure quality control, another reviewer undertook an independent second data extraction of a certain proportion of this review's selected studies, totaling 520 data points; 100% of these were the same and therefore it was concluded that the standard of data reliability was likely to be high.

RESULTS

The literature search returned 16 789 studies whose titles and abstracts were reviewed for relevance. 103 were selected for full text examination, however only 100 papers were sourced in full-text versions. Of these 31 were selected for inclusion in the review. In addition, 3 studies were found from other studies' reference lists and selected for inclusion, resulting in a total of 34 studies included in the review. Of these, 27 studies were deemed to be reporting data concerning CANS and 7 were considered to be less conclusive, possibly reporting neonatal sepsis acquired from another source (**Supplementary Table 6**) (50–56). To avoid potential compromising of final results it was decided to extract data from these 7 papers however exclude them from overall analyses. The literature search process is outlined in **Figure 2**.

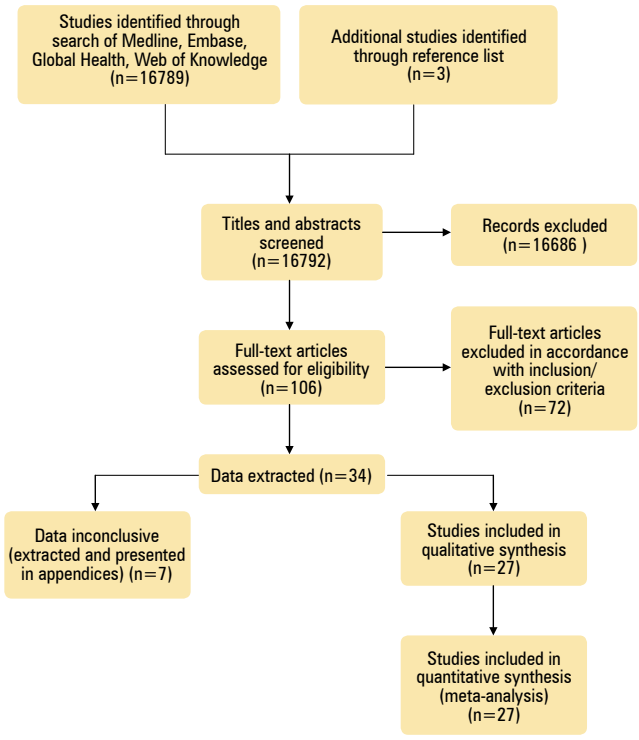


Figure 2 An overview of literature search results.

Table 2 Study characteristics

Characteristic		No. studies
WHO Region	Africa	11
	Americas	1
	Europe	2
	Eastern Mediterranean	1
	South-East Asia	7
	Western Pacific	5
Length of study	< 1 Year	3
	1–2 Years	9
	3–4 Years	8
	≥ 5 Years	5
	Not reported	2
Number of studies active in particular time periods	1980–1985	2
	1986–1990	5
	1991–1995	13
	1996–2000	11
	2001–2005	10
	2006–2010	2
	Not reported	2
Culture category	Blood	16
	CSF	5
	Blood and/or CSF*	5
	Urine/Other	2
Study denominator	Isolates	8
	Patients	19
Number of positive isolates	0–25	8
	26–50	10
	51–75	5
	76–100	1
	101–200	1
	>200	2
Number of potentially pathogenic positive isolates	0–25	11
	26–50	10
	51–75	3
	76–100	1
	101–200	1
	>200	1

CSF – cerebrospinal fluid

*One study also used antigen detection.

Characteristics of the studies that were retained after the process of literature search as they met the minimum quality criteria are shown in **Table 2**. A full version of this table can be found in **Supplementary Table 1**. Of the 27 studies, only 2 presented community surveillance data. Another 20 either presented CANS-specific or disaggregated non-nosocomial data and the remaining 5 did not explicitly report CANS aetiology but were deemed suitable for inclusion due to the infection type or study setting reported. Four studies were the primary data sources for a WHO Young Infants Study Group Multicenter Study (47), which presented overall data. However, in our study we treated each site as an independent data point, and we analysed the information from each study individually.

Aetiological data

Individual aetiological data from each study are presented in **Supplementary Table 2**. For the purpose of analyses, aetiological data were split by WHO regions, and then by age-of-onset. **Table 3** is a summary table that contains data for all isolated organisms by region. **Table 4** contains data for all potential pathogens isolated by region, both for age-of-onset categories ≤7 days of life and 8–59 days. Data for the 60–90 days of life category were excluded from these tables to fit with the WHO 'young infant' criteria. Full tables including this data are presented in **Supplementary Table 4**.

Figures 3 and 4 present the meta-analysis forest plot graphs for the potentially pathogenic Gram-positive and Gram-negative categories respectively. Forest plot graphs for all other potential pathogens are presented in **Supplementary Table 5**.

The percentages from **Table 4** on the six most commonly isolated organisms along with Group B *Streptococci* (GBS) are then illustrated in **Figure 5**. Group B *Streptococci* was included despite its relatively low prevalence so as to provide comparison with known high colonization rates experienced in many developed countries (57). **Figure 6** dis-

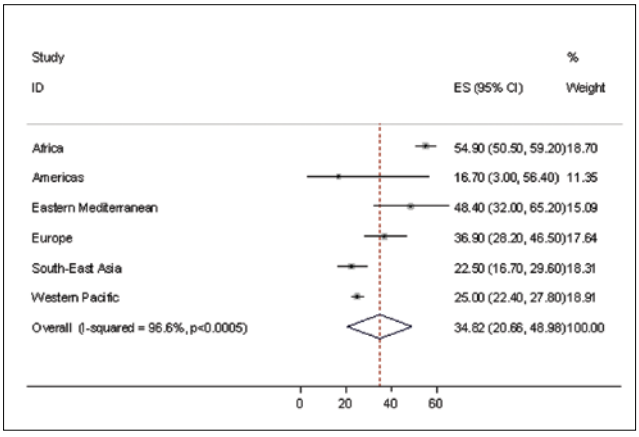


Figure 3 Forest plot of the summary estimate and 95% confidence interval of the prevalence of potentially pathogenic Gram-positives. Analysis is based on 27 studies in the 5 WHO regions (Africa: 11 studies, Americas: 1 study, Europe: 2 studies, Eastern Mediterranean: 1 study, South East Asia: 7 studies and Western Pacific: 5 studies). Weights are from random effects analysis. ES: estimate, 95% CI: 95% confidence interval; I-squared and p-value are measures for heterogeneity between the studies.

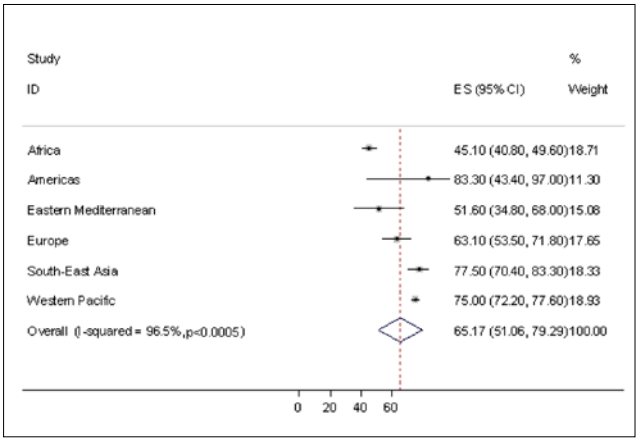


Figure 4 Forest plot of the summary estimate and 95% confidence interval of the prevalence of potentially pathogenic Gram-negatives. Analysis is based on 27 studies in the 5 WHO regions (Africa: 11 studies, Americas: 1 study, Europe: 2 studies, Eastern Mediterranean: 1 study, South East Asia: 7 studies and Western Pacific: 5 studies). Weights are from random effects analysis. ES: Estimate, 95% CI: 95% confidence interval; I-squared and p-value are measures for heterogeneity between the studies.

Table 3 Distribution of all microorganisms isolated by region

	Africa		Americas		Eastern Mediterranean		Europe		South-East Asia		Western Pacific		All Regions			
Microorganism isolated	N	% (95%CI)	N	% (95%CI)	N	% (95%CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	Median	IQ range
Staphylococcus aureus	85	14.6 (11.7–17.4)	0	0.0 (–)	0	0.0 (–)	28	26.4 (19.0–35.6)	20	10.0 (6.6–14.9)	168	15.2 (13.2–17.5)	301	14.6 (13.1–16.2)	12.3	12.6
Group A *Streptococci/ Streptococcus pyogenes*	40	6.9 (4.8–8.9)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	2	1.0 (0.3–3.6)	12	1.1 (0.6–1.9)	54	2.6 (2.0–3.4)	0.5	1.1
Group B *Streptococci*	40	6.9 (4.8–8.9)	0	0.0 (–)	0	0.0 (–)	1	0.9 (0.2–5.2)	6	3.0 (1.4–6.4)	3	0.3 (0.1–0.8)	50	2.4 (1.8–3.2)	0.6	2.4
Group D *Streptococci/ Enterococcus*	4	0.7 (0.0–1.4)	0	0.0 (–)	2	4.8 (1.3–15.8)	9	8.5 (4.5–15.4)	0	0.0 (–)	2	0.2 (0.0–0.7)	17	0.8 (0.5–1.3)	0.4	3.7
Streptococcus pneumoniae	81	13.9 (11.1–16.7)	1	3.0 (0.5–15.3)	3	7.1 (2.5–19.0)	0	0.0 (–)	7	3.5 (1.7–7.0)	14	1.3 (0.8–2.1)	106	5.1 (4.3–6.2)	3.3	4.5
Other/unspecified *Streptococcus* species	19	3.3 (2.1–5.0)	0	0.0 (–)	10	23.8 (13.5–38.5)	0	0.0 (–)	1	0.5 (0.1–2.8)	44	4.0 (3.0–5.3)	74	3.6 (2.9–4.5)	1.9	3.7
Other/ unspecified Gram-positives*	1	0.2 (0.0–1.0)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	1	0.5 (0.1–2.8)	110	10.0 (8.3–11.9)	112	5.4 (4.5–6.5)	0.1	0.4
Total Gram-positives	**270**	**46.3 (42.3–50.4)**	**1**	**3**	**15**	**35.7 (23.0–50.8)**	**38**	**35.8 (27.4–45.3)**	**37**	**18.5 (13.7–24.5)**	**353**	**32.0 (29.3–34.8)**	**714**	**34.6 (32.5–36.6)**	**33.9**	13.9
Klebsiella pneumoniae	22	3.8 (2.5–5.6)	0	0.0 (–)	2	4.8 (1.3–15.8)	20	18.9 (12.6–27.4)	67	33.5 (27.3–40.3)	143	13.0 (11.1–15.1)	254	12.3 (10.9–13.8)	8.9	13.4
Other/unspecified *Klebsiella* species	20	3.4 (2.2–5.2)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	5	2.5 (1.1–5.7)	0	0.0 (–)	25	1.2 (0.8–1.8)	0	1.9
Escherichia coli	64	11.0 (8.7–13.8)	0	0.0 (–)	3	7.1 (2.5–9.0)	38	35.8 (27.4–45.3)	18	9.0 (5.8–13.8)	243	22.1 (19.7–24.6)	366	17.7 (16.1–19.4)	10	11.7
Pseudomonas species	22	3.8 (2.5–5.6)	0	0.0 (–)	4	9.5 (3.8–22.1)	4	3.8 (1.5–9.3)	18	9.0 (5.8–13.8)	140	12.7 (10.9–14.8)	188	9.1 (7.9–10.4)	6.4	5.6
Enterobacter species	5	0.9 (0.4–2.0)	0	0.0 (–)	4	9.5 (3.8–22.1)	1	0.9 (0.2–5.2)	3	1.5 (0.5–4.3)	56	5.1 (4.0–6.5)	69	3.3 (2.6–4.2)	1.2	3.3
Serratia species	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	1	0.9 (0.2–5.2)	0	0.0 (–)	39	3.5 (2.6–4.8)	40	1.9 (1.4–2.6)	0	0.7
Proteus species	9	1.5 (0.8–3.0)	0	0.0 (–)	0	0.0 (–)	1	0.9 (0.2–5.2)	0	0.0 (–)	3	0.3 (0.1–0.8)	13	0.6 (0.4–1.1)	0.1	0.8
Salmonella species	17	2.9 (1.8–4.6)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	3	1.5 (0.5–4.3)	7	0.6 (0.3–1.3)	27	1.3 (0.9–1.9)	0.3	1.3
Haemophilus influenzae	25	4.3 (2.9–6.3)	3	9.1 (3.1–23.6)	1	2.4 (0.4–12.3)	0	0.0 (–)	1	0.5 (0.1–2.8)	2	0.2 (0.0–0.7)	32	1.5 (1.1–2.2)	1.4	3.6
Neisseria meningitidis	11	1.9 (1.1–3.3)	2	6.1 (1.7–19.6)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	13	0.6 (0.4–1.1)	0	1.4
Acinetobacter species	26	4.5 (3.1–6.5)	0	0.0 (–)	2	4.8 (1.3–15.8)	0	0.0 (–)	9	4.5 (2.4–8.3)	95	8.6 (7.1–10.4)	132	6.4 (5.4–7.5)	4.5	3.6
Other/unspecified Gram-negatives**	59	10.1 (7.9–12.8)	0	0.0 (–)	11	26.2 (15.3–41.1)	0	0.0 (–)	11	5.5 (3.1–9.6)	20	1.8 (1.2–2.8)	101	4.9 (4.0–5.9)	3.7	8.5
Total Gram-negatives	**280**	**48.0 (44.0–52.1)**	**5**	**15.2 (6.7–31.0)**	**27**	**64.3 (49.1–77.0)**	**65**	**61.3 (51.8–70.0)**	**135**	**67.5 (60.7–73.6)**	**748**	**67.9 (65.1–70.6)**	**1260**	**61.0 (58.9–63.1)**	**62.8**	15.3
Non-stated/Undetermined	33	5.7 (4.1–7.8)	27	81.8 (65.6–91.4)	0	0.0 (–)	3	2.8 (1.0–8.0)	28	14.0 (9.9–19.5)	1	0.1 (0.0–0.5)	92	4.5 (3.6–5.4)	4.2	11.1
Total	**583**	**100.0 (n/a)**	**33**	**100.0 (n/a)**	**42**	**100.0 (n/a)**	**106**	**100.0 (n/a)**	**200**	**100.0 (n/a)**	**1102**	**100.0 (n/a)**	**2066**	**100.0 (n/a)**		

95% CI – 95% confidence interval, IQ range – interquartile range

* Includes data *for Aerococcus* sp., *Bacillus* sp. and others.

**Includes data for *Citrobacter* sp., *Moraxella* sp., *Shigella* sp., *Aeromonas* sp. and others. Data was also extracted for coagulase-negative *Staphylococci*: Africa – 28 isolates, Americas – 0 isolates, Eastern Mediterranean – 0 isolates, Europe – 9 isolates, South-East Asia – 35 isolates, Western Pacific – 811 isolates.

Table 4 Distribution of potential pathogens isolated by region

	Africa		Americas		Eastern Mediterranean		Europe		South-East Asia		Western Pacific		All Regions			
Potential pathogen isolated	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	Median % (IQ range)	Meta-analysis % (95% CI)	P-value for heterogeneity
Staphylococcus aureus	85	17.3 (14.3–21.0)	0	0.0 (–)	0	0.0 (–)	28	27.2 (19.5–36.5)	20	12.5 (8.2–18.5)	168	17.3 (15.1–19.8)	301	17.1 (15.4–18.9)	14.9 (14.2)	17.4 (13.9–20.9)	0.036
Group A *Streptococci/ Streptococcus pyogenes*	40	8.2 (6.1–10.9)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	2	1.3 (0.3–4.4)	12	1.2 (0.7–2.1)	54	3.1 (2.4–4.0)	0.6 (1.2)	3.4 (0.0–7.2)	<0.0005
Group B *Streptococci*	40	8.2 (6.1–10.9)	0	0.0 (–)	0	0.0 (–)	1	1.0 (0.2–5.3)	6	3.8 (1.7–7.9)	3	0.3 (0.1–0.9)	50	2.8 (2.1–3.7)	0.6 (3)	3.2 (0.0–7.0)	<0.0005
Group D *Streptococci/ Enterococcus*	4	0.8 (0.3–2.1)	0	0.0 (–)	2	6.5 (1.8–20.7)	9	8.7 (4.7–15.8)	0	0.0 (–)	2	0.2 (0.1–0.7)	17	1.0 (0.6–1.5)	0.5 (5)	1.1 (0.0–2.5)	0.007
Streptococcus pneumoniae	81	16.5 (13.5–20.1)	1	16.7 (3.0–56.4)	3	9.7 (3.3–24.9)	0	0.0 (–)	7	4.4 (2.1–8.8)	14	1.4 (0.9–2.4)	106	6.0 (5.0–7.2)	7 (12.6)	8.3 (0.8–15.9)	<0.0005
Other/unspecified *Streptococcus* species	19	3.9 (2.5–6.0)	0	0.0 (–)	10	32.3 (18.6–49.9)	0	0.0 (–)	1	0.6 (0.1–3.5)	44	4.5 (3.4–6.0)	74	4.2 (3.4–5.2)	2.3 (4.2)	4.1 (0.9–7.3)	<0.0005
Potentially pathogenic Gram-positives	**269**	**54.9 (50.5–59.2)**	**1**	**16.7 (3.0–56.4)**	**15**	**48.4 (32.0–65.2)**	**38**	**36.9 (28.2–46.5)**	**36**	**22.5 (16.7–29.6)**	**243**	**25.0 (22.4–27.8)**	**602**	**34.2 (32.0–36.4)**	31 (22.4)	34.8 (20.7–49.0)	<0.0005
Klebsiella species	42	8.6 (6.4–11.4)	0	0.0 (–)	2	6.5 (1.8–20.7)	20	19.4 (12.9–28.1)	72	45.0 (37.5–52.7)	143	14.7 (12.6–17.1)	279	15.8 (14.2–17.6)	11.6 (11.3)	18.6 (9.9–27.3)	<0.0005
Escherichia coli	64	13.1 (10.4–16.3)	0	0.0 (–)	3	9.7 (3.3–24.9)	38	36.9 (28.2–46.5)	18	11.3 (7.2–17.1)	243	25.0 (22.4–27.8)	366	20.8 (19.0–22.7)	12.2 (12)	19.1 (11.1–27.1)	<0.0005
Pseudomonas species	22	4.5 (3.0–6.7)	0	0.0 (–)	4	12.9 (5.1–28.9)	4	3.9 (1.5–9.6)	18	11.3 (7.2–17.1)	140	14.4 (12.3–16.8)	188	10.7 (9.3–12.2)	7.9 (8.5)	9 (3.5–14.5)	<0.0005
Enterobacter species	5	1.0 (0.4–2.4)	0	0.0 (–)	4	12.9 (5.1–28.9)	1	1.0 (0.2–5.3)	3	1.9 (0.6–5.4)	56	5.8 (4.5–7.4)	69	3.9 (3.1–4.9)	1.4 (3.8)	2.9 (0.2–5.6)	<0.0005
Serratia species	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	1	1.0 (0.2–5.3)	0	0.0 (–)	39	4.0 (3.0–5.4)	40	2.3 (1.7–3.1)	0 (0.7)	N/a (only 2 studies)	–
Proteus species	9	1.8 (1.0–3.5)	0	0.0 (–)	0	0.0 (–)	1	1.0 (0.2–5.3)	0	0.0 (–)	3	0.3 (0.1–0.9)	13	0.7 (0.4–1.3)	0.2 (0.8)	0.5 (0.1–0.8)	0.07
Salmonella species	17	3.5 (2.2–5.5)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	3	1.9 (0.6–5.4)	7	0.7 (0.3–1.5)	27	1.5 (1.1–2.2)	0.4 (1.6)	1.9 (0.0–3.9)	0.006
Haemophilus Influenzae	25	5.1 (3.5–7.4)	3	50.0 (18.8–81.2)	1	3.2 (0.6–16.2)	0	0.0 (–)	1	0.6 (0.1–3.5)	2	0.2 (0.1–0.7)	32	1.8 (1.3–2.6)	1.9 (4.3)	2.3 (0.0–5.3)	<0.0005
Neisseria Meningitidis	11	2.2 (1.3–4.0)	2	33.3 (9.7–70.0)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	13	0.7 (0.4–1.3)	0 (1.7)	N/a (only 2 studies)	–
Acinetobacter species	26	5.3 (3.7–7.7)	0	0.0 (–)	2	6.5 (1.8–20.7)	0	0.0 (–)	9	5.6 (3.0–10.3)	95	9.8 (8.1–11.8)	132	7.5 (6.4–8.8)	5.5 (4.9)	7 (4.0–10.0)	0
Potentially pathogenic Gram-negatives	**221**	**45.1(40.8–49.6)**	**5**	**83.3 (43.4–97.0)**	**16**	**51.6**	**65**	**63.1**	**124**	**77.5 (70.4–83.3)**	**728**	**75.0 (72.2–77.6)**	**1159**	**65.8 (63.6)**	69 (22.4)	65.2 (51.1–79.3)	<0.0005
Total	**490**	**100.0 (n/a)**	**6**	**100.0 (n/a)**	**31**	**100**	**103**	**100.0 (n/a)**	**160**	**100.0 (n/a)**	**971**	**100.0 (n/a)**	**1761**	**100.0 (n/a)**			

95% CI – 95% confidence interval, IQ range – interquartile range

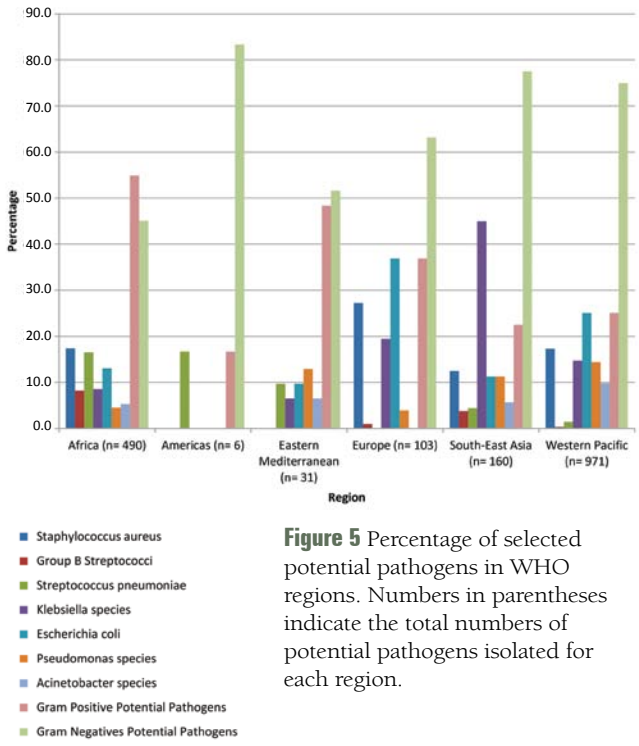


Figure 5 Percentage of selected potential pathogens in WHO regions. Numbers in parentheses indicate the total numbers of potential pathogens isolated for each region.

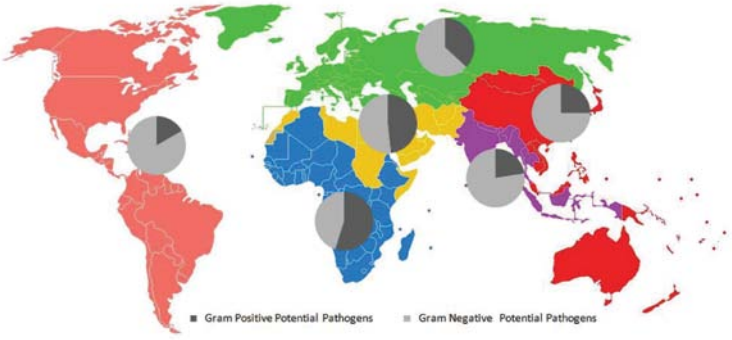


Figure 6 Distribution of Gram-positive and Gram-negative potential pathogens by region.

plays data from **Table 4** of the relative proportions of gram-positive and gram-negative potential pathogens in each region.

Table 5 presents data of all organisms isolated in all regions categorised by different age-of-onset categories. Region-specific age-of-onset data for potential pathogens are presented in **Supplementary Table 3**. Eight studies from 6 countries in 4 regions (Africa, Europe, South-East Asia, Western Pacific) reported data for the category of neonates who were up to 7 days old. Data were presented in varying ways and in addition to aetiological data specified as sepsis occurring at ≤7 days of life, data reported as 4–6 days, 0–6 days, 0–7 days, 0–5 days and 'early-onset' were also included in this category.

However, all studies (from 14 countries, and in all regions) reported data for the category of neonates and young infants who were 8–59 days old. In addition to aetiological data specified as sepsis occurring at 8–59 days of life, data categorised as <2 months, 1–2 months, 8–60 days, 8–30 days, 7–59 days, 7–55 days, 7–28 days and 'late-onset' or being from 'neonates/newborns' were also included. Finally, five studies from five countries in two regions (Africa, Western Pacific) reported data for the category of infants 60–90 days of age. In addition to aetiological data specified as sepsis occurring at 60–90 days of life, data categorised as 2–3 months, 31–90 days, 30–90 days, 30–59 days and 1–3 months were also included.

Study denominator

Nineteen studies used patients as a denominator, while 8 used isolates. Data on potential pathogens from all age-of-onset categories and regions were split into those 2 groupings and displayed in **Figures 7 and 8**, respectively.

Other reported information

Ten studies from 8 countries in four regions reported data on CANS-specific case fatality rates, and these are detailed in **Table 6** which furthermore contains CANS-specific incidence data reported by 3 studies. With regard to the commonly reported risk factors for neonatal sepsis among premature or low birth weight neonates, only a single source of data was identified for each. Gatchalian and co-workers reported 46% incidence of CANS in low birth weight infants in low resource settings (43), while Mondal and co-workers quoted 22% of CANS incidence occuring in preterm neonates (38). Culture positivity rates varied significantly, with reported rates as high as 65% (41) and as low as 5% (26), or even 3% for some age groups (24). This could suggest significant differences among studies in inclusion criteria, case definition or capacity for accurate microbiological analysis, and therefore potentially data quality. Finally, 6 studies reported data concerning CANS-specific antimicrobial sensitivity patterns. Sensitivity percentages to selected antimicrobials for the most prevalent pathogens are displayed in **Table 7**.

DISCUSSION

The overall data on CANS in low and middle income countries are very limited, with only 27 studies suitable for inclusion, many of which had small sample sizes and provided little data. This suggests a degree of caution over the overall validity of the review's results. There was also significantly fewer data for the age-of-onset categories ≤7 days of life and 60–90 days of life. The geographic focus of studies in certain global regions is another concern, with 17 of 28 studies taking place in Africa or South-East Asia regions.

Table 5 Distribution of all isolates by age-of-onset

	≤7 days of life		8–59 days of life		60–90 days of life	
Organism Isolated	N	% (95% CI)	N	% (95%CI)	N	% (95%CI)
Staphylococcus aureus	33	11.7 (8.0–15.5)	268	15.0 (13.4–16.7)	1	2.3 (0.0–6.7)
Group A *Streptococci/ Streptococcus pyogenes*	4	1.4 (0.0–2.8)	50	2.8 (2.0–3.6)	8	18.2 (6.8–29.6)
Group B *Streptococci*	19	6.7 (3.8–9.7)	31	1.7 (1.1–2.4)	0	0.0 (–)
Group D *Streptococci/ Enterococcus*	4	1.4 (0.0–2.8)	13	0.7 (0.3–1.1)	0	0.0 (–)
Streptococcus Pneumoniae	13	4.6 (2.1–7.1)	93	5.2 (4.2–6.3)	14	31.8 (18.1–45.6)
Other/unspecified *Streptococcus* species	24	8.5 (5.3–11.8)	50	2.8 (2.0–3.6)	0	0.0 (–)
Other/ unspecified Gram-positives*	0	0.0 (–)	112	6.3 (5.2–7.4)	0	0.0 (–)
All Gram-positives	97	34.4 (28.9–39.9)	617	34.6 (32.4–36.8)	23	52.3 (37.5–67.0)
Klebsiella pneumoniae	22	7.8 (4.7–10.9)	232	13.0 (11.4–14.6)	2	4.5 (0.0–10.7)
Other/unspecified *Klebsiella* species	10	3.5 (1.4–5.7)	15	0.8 (0.4–1.3)	0	0.0 (–)
Escherichia coli	46	16.3 (12.0–20.6)	320	17.9 (16.2–19.7)	1	2.3 (0.0–6.7)
Pseudomonas species	22	7.8 (4.7–10.9)	166	9.3 (8.0–10.7)	1	2.3 (0.0–6.7)
Enterobacter species	10	3.5 (1.4–5.7)	59	3.3 (2.5–4.1)	0	0.0 (–)
Serratia species	0	0.0 (–)	40	2.2 (1.6–2.9)	1	2.3 (0.0–6.7)
Proteus species	6	2.1 (0.4–3.8)	7	0.4 (0.1–0.7)	0	0.0 (–)
Salmonella species	1	0.4 (0.0–1.0)	26	1.5 (0.9–2.0)	6	13.6 (3.5–23.8)
Haemophilus influenzae	2	0.7 (0.0–1.7)	30	1.7 (1.1–2.3)	4	9.1 (0.6–17.6)
Neisseria meningitidis	0	0.0 (–)	13	0.7 (0.3–1.1)	0	0.0 (–)
Acinetobacter species	19	6.7 (3.8–8.7)	113	6.3 (5.2–7.5)	3	6.8 (0.0–14.3)
Other/unspecified Gram-negatives**	42	14.9 (10.7–19.0)	59	3.3 (2.5–4.1)	1	2.3 (0.0–6.7)
All Gram-negatives	180	63.8 (58.2–69.4)	1080	60.5 (58.3–62.8)	19	43.2 (28.5–57.8)
Non-stated/Undetermined	5	1.8 (0.2–3.3)	87	4.9 (3.9–5.9)	2	4.5 (0.0–10.7)
Totals	282	100.0 (n/a)	1784	100.0 (n/a)	44	100.0 (n/a)

*Includes data for *Aerococcus* sp., *Bacillus* sp. and others.
** Includes data for *Citrobacter* sp., *Moraxella* sp., *Shigella* sp., *Aeromonas* sp. and others. Data were also extracted for coagulase- negative *Staphylococci*: ≤7 days of life – 3 isolates, 7–59 days of life – 880 isolates, 60–90 days of life – 0 isolates.

Table 6 Reported case fatality rates and incidence data

Region	Article	Case fatality rate reported*	Incidence data reported
Africa	Berkley *et al* (22)	56% of ≤7 days of life, 26% of 8–59 days of life	1457/10^5 person years (for infants <1year old)
	Mulholland *et al* (28)	31% of 0–91 days of life	–
	English *et al* (24)	27% of ≤7 days of life, 5% of 8–59 days of life	–
	Muhe *et al* (27)	49% of 0–59 days of life	–
	Campagne *et al* (23)	58% of 0–59 days of life	–
Americas	Weiss *et al* (30)	–	421/10^5 person years (for infants <2months old)
South-East Asia	Mondal *et al* (38)	32% of 0–59 days of life	–
	Mathur *et al* (37)	70% of 0–59 days of life	–
Europe	Taskin *et al* (33)	5% of ≤7 days of life, 3% of 8–59 days of life	–
Western Pacific	Quiambao *et al* (45)	29% of 0–91 days of life	–
	Gatchalian *et al* (43)	26% of 0–91 days of life	–
	Choo *et al* (42)	–	1571/10^5 live births

*Data were standardised to fit with age categories used in review.

Although the majority of studies being conducted in Africa can be argued to fit with Africa having the highest neonatal mortality rates globally, it should be noted that seven out of ten African studies were based in Nigeria or Kenya, and there were little or no data for other countries with comparable neonatal mortality levels. Similarly, 6 out of 7 South-East Asian studies were conducted in India, which again has high neonatal mortality rates. However, these are reportedly lower than in Pakistan, yet no studies were found from Pakistan (58).

The largest numbers of studies found by this review were conducted between 1991 and 1995 and only 2 studies were relevant to the most recent period of 2006–2010, highlighting the need for new research in this area and implying potential issues with the representativeness of data presented here. Excluding studies before 1980 to narrow the literature review may have resulted in missing some relevant studies. Although the search was systematic, some studies after 1980 may have also been missed due to the potential of human error in screening results. In addition, several foreign language studies were excluded because it was not possible to extract enough information to include them in the review. Several studies had very low culture positivity rates, resulting in small numbers of organisms being reported. The potential to generalise results is limited by their small sample sizes. Some studies presented considerably larger numbers of isolated organisms than

others, thereby giving greater weight to their reported aetiological data.

To analyse aetiological data by the age-of-onset, it was necessary to standardise data into specific categories; however, these categories did not always fit with reported data. In certain cases it was therefore necessary to reassign and impute data. This was not the case for the significant majority of studies. Despite some of the limitations described above, data presented in this review should be generally robust and useful for planning international child health policy on tackling neonatal infections.

Study design

Criteria for diagnosing neonatal sepsis varied significantly, providing inconsistencies in data and potential biases. Some studies included pneumonia and meningitis in this category, while others considered them indistinguishable from the data for sepsis. The criteria for excluding nosocomial infections also differed, with several studies merely separating data into babies born in the study hospital and babies born elsewhere (and other studies not defining criteria at all). The age-of-onset categories also were not fully consistent between studies, and there were some discrepancies with definitions of 'early-onset' and 'late-onset' sepsis. Several studies did not collect data for all age-of-onset categories, therefore not providing a complete picture of CANS aetiology. Also, a certain number of studies split data into community-acquired and nosocomial, and into different age-of-onset categories, but they did not combine these two categorisations. Still, in all cases we used the information from other studies to impute the data and align it with the majority of studies, in order to prevent valuable information from being lost.

Although several studies explicitly reported excluding infants who had received prior antimicrobial therapy, the majority of studies did not report inclusion or exclusion criteria relating to this factor. This is potentially an important issue as antimicrobial therapy prior to blood cultures being taken could significantly change aetiological patterns and therefore bias the reported data. Most studies reported data from babies who presented to primary facilities or outpatient services of referral facilities. The aetiological distribution may differ from that of babies who are born at home and die before reaching hospital. Only two studies adopted a community-surveillance approach that could counter this issue.

Culture positivity rates were reported to be considerably low by some studies, potentially indicating inadequate laboratory facilities or high prior antimicrobial use. Future reviews could potentially exclude these studies, but this would further decrease the amount of data. It is likely that the prevalence of certain pathogens such as *Haemophilus influenzae* is underestimated in many studies due to the significant diagnostic capacity required to isolate these organisms (4). For the same reason, it is possible that prevalence of less fastidious organisms such as *S. aureus* is overestimat-

Table 7 Percentage sensitivity patterns of most prevalent pathogens to selected antimicrobials

	Region	Africa		South-East Asia			
Organism	Antimicrobial	Adejuyigbe *et al* (20)	Muhe *et al* (27)	Mathur *et al* (37)	Panigrahi *et al* (39)	Darmstadt *et al* (35)	Tallur *et al* (41)
Escherichia coli	Amoxycillin (AMX)	60.0	–	–	–	–	–
	Ampicillin (AMP)	40.0	100.0	–	–	100.0	29.0
	Cefotaxime (CTX)	–	–	–	–	–	100.0
	Ceftazidime (CAZ)	–	100.0	–	–	100.0	–
	Ceftriaxone (CRO)	–	–	–	–	100.0	100.0
	Ciprofloxacin (CIP)	–	–	–	–	100.0	–
	Gentamicin (GEN)	80.0	100.0	–	–	100.0	71.0
	Imipenem (IMP)					100.0	–
Staphylococcus aureus	Amoxycillin (AMX)	73.0	–	–	–	–	–
	Ampicillin (AMP)	–	–	–	–	0.0	21.0
	Cefotaxime (CTX)	–	–	–	–	–	–
	Ceftazidime (CAZ)	–	–	–	–	66.7	–
	Ceftriaxone (CRO)	–	–	–	–	90.0	–
	Ciprofloxacin (CIP)	–	–	–	–	80.0	–
	Gentamicin (GEN)	85.8	–	–	–	90.0	29.0
	Imipenem (IMP)	–	–	–	–	90.0	–
Klebsiella species*	Amoxycillin (AMX)	0.0	–	–	–	–	–
	Ampicillin (AMP)	–	–	10.0	–	0.0	25.5
	Cefotaxime (CTX)	–	–	–	–	–	76.5
	Ceftazidime (CAZ)	–	–	–	22.0	33.3	–
	Ceftriaxone (CRO)	–	–	71.4	–	33.3	81.0
	Ciprofloxacin (CIP)	–	–	64.8	11.0	66.7	–
	Gentamicin (GEN)	100.0	–	42.8	–	66.7	59.5
	Imipenem (IMP)	–		100.0	–	100.0	–

*Averages were taken when more than one variant's sensitivity patterns were reported.

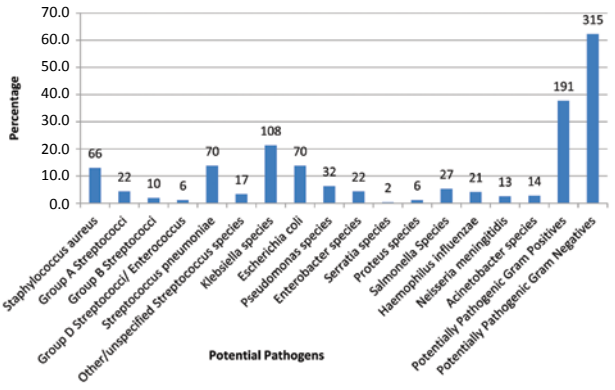


Figure 7 Potential pathogens in studies using patients as denominator. Data labels indicate the number of isolates.

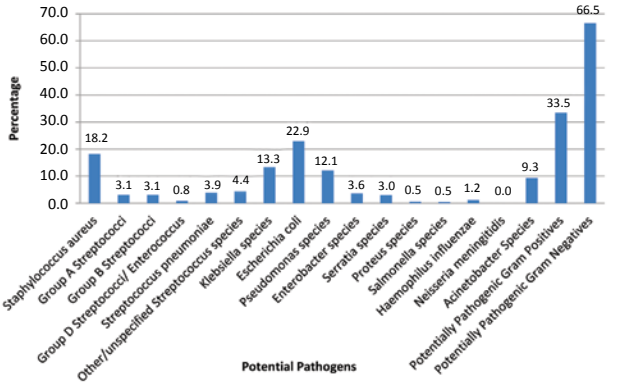


Figure 8 Potential pathogens in studies using isolates as denominator. Data labels indicate the number of isolates.

ed, due to comparitive ease of isolation. This is reinforced by a study that used the non-culture technique of antigen detection and reported significantly higher *H. influenzae* prevalence compared with many other studies (30).

Distribution of CANS pathogens in developing countries

This review suggests that the majority of organisms that cause CANS in low and middle income countries are Gram-negative pathogens. The most commonly isolated are, in ranked order, *S. aureus, E. coli* and *Klebsiella* species. These results are similar to a previous review, where the order of prevalence was *Klebsiella* species, *E. coli* and *S. aureus* (4). The potential for significant comparisons of the regional distribution of potential pathogens is limited due to the paucity of data, particularly in the Eastern Mediterranean and Americas regions. Both Europe and Western Pacific regions are similar to the overall distribution with *S. aureus, E. coli* and *Klebsiella* species the most prevalent organisms. The Western Pacific region also displays a higher prevalence of *Pseudomonas* species compared with overall aggregates. Europe has a high prevalence of Group D *Streptococci*. In the African region, *S. aureus* is seen as the most prevalent potential pathogen, followed by *Streptococcus pneumoniae,* which is only marginally less prevalent and is found in all age-of-onset categories. Notably, the prevalence of both Group A and Group B *Streptococci* is more than doubled in comparison to other regions. In the African region, unlike in any other region, 54.9% of potential pathogens isolated were Gram-positive. The Eastern Mediterranean region also showed a relatively high prevalence with 48% Gram-positive potential pathogens. This is important to consider, as some antibiotics are more effective against one than the other. South-East Asian region displayed a major predominance of *Klebsiella* species, followed by *S. aureus, E. coli* and *Pseudomonas* species.

Although the distribution of potential pathogens is broadly similar in ≤7 days of life and 8–59 days of life, GBS isolates are notably more prevalent in the ≤7 days of life category. This was potentially expected, as neonatal GBS infection is commonly taken to be maternally-acquired (59). This review reports a lower prevalence of GBS as a CANS pathogen in developing countries than previous research (4). However, the prevalence of GBS neonatal sepsis in the first 7 days of life estimated by both this paper and previous review (4) is considerably lower than in developed countries (60). It is unclear whether a genuine aetiological difference is present, or there is a bias because most cases of early-onset sepsis in developing countries are not being registered because infants die before reaching health facilities (61). This is potentially supported by Stoll and Schuchat, who reported similar rates of maternal GBS colonization in developing countries compared with developed countries (62). Culture-negative GBS neonatal sepsis has also been shown in previous studies to be high, potentially as a result of maternal antibiotic therapy (63). This could result in underestimation of the burden of GBS neonatal sepsis if based on bacterial isolates.

The predominance of Gram-negative organisms and overall similar distribution of pathogens in the ≤7 days of life and the 8–59 days of life age-of-onset categories may contradict the assumption that early-onset neonatal sepsis is mainly maternally acquired. One potential explanation for these similar distributions is bias resulting from the necessary standardisation of primary data for analysis. However, this notion was also supported by another systematic review (4) and therefore may potentially have implications for CANS prevention, highlighting the need for improved hygienic practices before, during and after birth. In addition, similar aetiologies between the two groups may suggest that WHO 'young infant' guidelines (7–59 days) for management of sepsis could also be used for sepsis occurring before this period.

Data for the post-young infant category of 60–90 days of life showed marked differences compared with that of earlier age-of-onset categories, justifying the 7–59 day age group defined in WHO 'young infant' guidelines, because management is likely to be different for later ages-of-onset. There was a significantly higher relative prevalence of Group A *Streptococci*, *S. pneumoniae*, *Salmonella* species and *H. influenzae*, and an overall majority of Gram-positive organisms, as compared with the significant Gram-negative majorities in other categories. One potential reason for this may be a bias due to the small quantity of data for this category. However, similar aetiological distributions are reported by Zaidi et al. (4) and this notion could be of significance and relevant for informing antibiotic therapy.

CANS compared with hospital-acquired neonatal sepsis

A recent review of hospital-acquired neonatal sepsis in developing countries showed a predominance of Gram-negative organisms with *Klebsiella* species most commonly isolated, followed by *S. aureus* and then *E. coli* (5). This is similar to this review's findings, suggesting potential similarities in major pathogens between CANS and hospital-acquired neonatal sepsis in developing countries. The hospital-acquired neonatal sepsis review, however, showed GBS as far more frequent causative organism than in this review of CANS. This may be due to easier capture of GBS in hospital-born babies as the vast majority of cases present within 48 hours of birth, whereas cases occuring in home-born babies may never have the opportunity to be diagnosed because of the fatal nature of this disease (60).

Incidence, case-fatality, risk factors, diagnosis and treatment

CANS-specific incidence was reported in only 3 papers (3 countries, 3 regions), and in different formats, ranging from 421/100 000 person years for infants under 2 months to 1571/100 000 live births. These data are insufficient to draw more general conclusions, and a similar lack of data was highlighted in a recent review of the burden of neonatal infections in developing countries (64). Lack of healthcare access and low levels of care-seeking lead to significantly underestimation of CANS incidence in most studies (65), although community surveillance study designs may go some way to ameliorate this.

Data on Case Fatality Rates (CFRs) were also scarce, presented in only 10 studies (8 countries in 4 regions), with no data from the Americas and Eastern Mediterranean regions. The potential for comparison of CFRs is also limited as they are significantly dependant on age-of-onset and severity. However, the majority of studies reported CFRs of over 30%, with the overall CFR for developing countries seen to be as much as 20 times higher than that of developed countries. This is congruent with the estimate of 99% of neonatal deaths occurring in developing countries (1,60). Addressing reasons behind this gap and designing interventions to reduce its size are clear areas for policy development and implementation.

Comparing studies that used patients as a denominator with those that used isolates, the distribution of potential pathogens is generally similar. Studies using isolates displayed a higher prevalence of *S. aureus*, potentially reflecting multiple isolates for each patient rather than a difference in distribution. *S. pneumoniae* is significantly more prevalent in studies using patients as a denominator. This is most likely due to the fastidious nature of *S. pneumoniae*, which quickly autolyses in blood cultures, whereas *S. aureus* is a hardy pathogen and is known to be associated with prolonged bacteremia in many cases (66,67).

Only 2 studies reported data concerning CANS-specific risk factors (38,43). Data reported suggests that low birth weight and prematurity are both significant risk factors for CANS, but further risk factors should also be evaluated.

Six studies from two regions reported CANS-specific data on pathogen antimicrobial sensitivity. Data reported suggests the main area of concern regarding antibiotic resistance is that of *Klebsiella* species, which did not have 100% of isolates sensitive to any antibiotic apart from imipenem, and had high rates of resistance to third generation cephalosporins and aminoglycosides. This is a significant point to consider for targeted antibiotic therapy, especially in the South-East Asian region where *Klebsiella* species account for 45% of CANS. There is a need for further surveillance to accurately determine the sensitivity patterns of CANS pathogens, thereby aiding appropriate therapy and minimising occurrence of resistance (17). Emerging antibiotic resistance is a global problem, and one potential reason for this is the wide availability of over-the-counter antibiotics in low and middle income countries (61). This is an important area to consider which to be combated requires both legislative and health promotion policies.

Coagulase-negative *Staphylococci* (CNS) were excluded as a contaminant in this and also in other reviews (4) and primary data sources (28), where no difference was reported in symptoms between patients with positive CNS blood cultures and those with entirely negative blood cultures (implying no pathogenicity). Conversely, in developed countries CNS are cited as major causative organisms of neonatal sepsis (60), although these data come from neonatal intensive care units and so further research is necessary to establish consensus on CNS pathogenicity with relation to CANS.

Overall data for the WHO Young Infants Study Group multicenter study (18) presented that 26% of *S. pneumoniae*

isolates were type 2, which is not included in current pneumococcal conjugate vaccines. It is suggested that further research should be conducted in this area to establish this finding's significance and inform future vaccination development and policy (18).

Implications for future research and international child health policy

This review has highlighted significant gaps in information concerning CANS in developing countries, and more research into this area is urgently required. Due to the small number of studies reporting CANS aetiology it is necessary to further evaluate results presented here, to determine whether they are specific to these studies or reflect genuine aetiological distributions. The number of studies presenting data concerning 2005–2010 is five times less than those presenting data for 2000–2010, which suggests that the interest in this type of research is decreasing.

Future research should focus on areas with high disease burden and a significant paucity of data, such as certain parts of South-East Asia and the Africa. Research into CANS occurring within the first 7 days of life is also significantly needed as approximately 75% of neonatal deaths occur within this period (58), yet aetiological data is particularly scarce. Based on characteristics and limitations of studies analysed in this review, it is recommended that all future studies into CANS aetiology in developing countries follow the minimum criteria presented in **Table 8**.

As a potential means of achieving greater and more representative data for CANS in developing countries the establishment of several community surveillance sites is recommended, equally situated in all WHO regions and providing coordinated multicentre research data using the criteria above (58). Significant investment would be required to ensure adequate surveillance, but this would be warranted because reducing neonatal mortality – particularly from infections – is crucial for progress towards Millennium Development Goal 4. Aetiological data from this review could be relevant when devising maternal and neonatal immunization strategies for developing countries. With mounting global levels of antibiotic resistance, immunization is becoming an increasingly important possible means of protecting neonates from infection (65). One potential approach is passive immunization through maternal vaccination for which vaccines against GBS, *S. pneumoniae* and *H. influenzae* are in development at present (68). Although vaccines against pathogens including Hepatitis B and Poliovirus are currently administered at birth in many countries, direct immunization of neonates is less well understood for the pathogens discussed in this review (69). There is also little current research into the use of established childhood vaccines such as pneumococcal or *H. influenzae* type-b (Hib) in the neonatal period, despite some positive previous indications (70). This review encourages more research in this area and also suggests the need for investigation into vaccination possibilities for other pathogens prevalent in CANS in developing countries. Data from this review specifically supports research into maternal and neonatal pneumococcal vaccination as *S. pneumoniae* was highly prevalent in Africa, including the very first week of life. Serological issues with the conjugate vaccine in neonates have however been highlighted above and these require further investigation.

This review also highlighted the need for identification, recognition and control of risk factors for CANS in developing countries. Low birth weight and prematurity are the only studied ones. Potential interventions to reduce the prevalence of these risk factors include improved maternal education and nutrition, prophylaxis/treatment of maternal malaria and other infections and overall improvement in socioeconomic conditions (71). Improved hygienic birth practices are also critical, emphasized by this review's suggestion that similar aetiological distributions between age categories may actually mean that most of the infections are acquired from the environment. In community settings,

Table 8 Minimum preferred criteria for future research

Criteria	Preferred standard
Study design	Community surveillance
Case definition/ inclusion criteria	Use Darmstadt *et al* (35) algorithm for community-based neonatal assessment and diagnosis. Confirm microbiologically.
	Exclude infants if received prior antimicrobial therapy.
	Use explicit criteria for exclusion of nosocomial infection.
Data set	Use explicitly defined age-of-onset categories from WHO IMCI* guidelines.
	Report site-of-birth of all cases.
	Use highest feasible standard of microbiology facilities.
	Record incidence per 10^5 live births in clearly defined study population.
	Record case fatality rates for microbiologically confirmed sepsis.
	Record data on risk factors.
	Study denominator should be patients.
	Test all isolates for antimicrobial sensitivity.

*WHO Integrated Management of Childhood Illness (16).

improvements in hygienic practices can be linked to community and maternal health education and the training of traditional birth attendants (65).

High case fatality rates reported in this review highlight the critical need for early diagnosis of severe neonatal illness for improving outcomes. There is a clear need for the improvement of current diagnostic methods and development of novel methods which would be feasible within the low resources settings. The WHO Integrated Management of Childhood Illness (IMCI) guidelines (16) use diagnostic algorithms to assess illness, an approach that is highly indicated in community settings where diagnostic facilities are limited. A specific community-setting evaluation of a similar diagnostic algorithm showed high sensitivity and specificity (72), therefore suggesting that algorithms present a significant potential for providing accurate community-based diagnosis. Investments in dissemination of knowledge in this area and potential resultant policy approaches are encouraged. However, due to the varying aetiological distributions and antibiotic sensitivities found in this review, the development of effective low-cost pathogen detection techniques is also implicated as therapy informed by this is likely to be more effective. The case for improved diagnostics is further emphasized by poor levels of culture positivity and suggestions of potentially biased information due to difficulties in isolating fastidious organisms.

Knowledge on aetiology is essential for appropriate and effective treatment. The regional and age-of-onset aetiological variation presented in this review could be of use for local, national or regional bodies when devising case management guidelines. Further research would provide a more current picture of aetiological distribution and allow for regular guideline updates. The significant differences in aetiology between regions shown in this review suggest the benefits of a regional, rather than global, approach to case management guidelines. This review also reports potentially significant antimicrobial resistance levels, especially among *Klebsiella* species, further supporting the need for community surveillance sites as suggested above to monitor emerging resistance and inform attempts to minimize it. Due to the nature of CANS it is necessary to investigate the possibilities for effective low-cost treatment that is simple to administer in a community setting. For an antibiotic regimen to be appropriate to community settings, efficacy and safety even at an extended-interval dosing regimen is a desirable attribute (73). Penicillins and cephalosporins potentially fulfil those criteria. However, further evaluation of the efficacy of these and other antibiotics in community settings and against the spread of pathogens reported in this review is necessary to provide accurate reccomendations of appropriate therapy for CANS.

There is noteworthy potential for the implementation of community-based care packages to reduce CANS incidence and resulting mortality. A trial in India involving hygienic birth practices, regular home visits, simple algorithms for detection of neonatal illness and referral to healthcare facilities, or community-based treatment using oral or parenteral antibiotic therapy, was shown to be highly effective (74). All interventions were conducted or overseen by trained community health personnel and were combined with community health education programmes including birth preparedness and promotion of preventative neonatal care practices. Based on comparison with control villages, the study reported a 70% reduction in neonatal mortality rates (74). This model has been replicated in other locations with similar successes, suggesting that its combination of community-based prevention, diagnosis and treatment could potentially provide a cost-effective and successful way of significantly reducing CANS incidence and mortality for many of the sites of studies analysed in this review (72,73,75,78). Implementation and evaluation of similar programmes could potentially be undertaken in conjunction with the community surveillance sites suggested above.

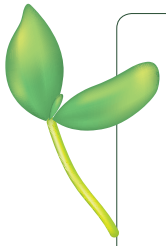
It must be noted that accurate data collection on aetiological distribution in low resource community settings can be a difficult task due to a lack of adequate microbiological facilities and trained staff (75). There are also considerable issues with the supply and quality of antimicrobials in certain developing areas (76) and a major requirement for accurate aetiological data and improved treatment in developing countries can be seen to be that of health system strengthening (77).

CONCLUSION

This systematic literature review of community-acquired neonatal sepsis (CANS) in developing countries suggests that the most common causative pathogens are *S. aureus, E. coli* and *Klebsiella* species, but with significant variation between regions and age-of-onset categories. This variation is important to monitor and consider for implementing appropriate therapy, devising management guidelines and informing related policy measures aimed at reducing CANS and overall neonatal mortality.

Several recommendations have been made to address issues highlighted by this paper. Data concerning the aetiology of CANS in developing countries are limited and significant future research is necessary, focusing on areas of high disease burden where there is a paucity of data. The establishment of community surveillance sites conducting co-ordinated research using minimum criteria is suggested to monitor CANS aetiology and chart antimicrobial sensitivity patterns. Other suggested areas of research include

investigations into neonatal immunization, risk factors for CANS and development of effective low-cost diagnostics for improving microbiologic results. Health system strengthening is needed to enable positive improvements in accurate aetiological data and CANS prevention and management. A reduction in overall neonatal mortality rates is important for achieving Millennium Development Goal 4 and there is a significant potential for the implementation of community-based care practices to achieve this with relation to CANS.



Acknowledgements: We thank Sheila Fisken, librarian, for her advice on databases and refining of search terms.

Funding: Bill and Melinda Gates Foundation.

Ethical approval: Not required.

Authorship declaration: All authors designed and conducted the study and contributed to writing the paper.

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 support from Bill and Melinda Gates Foundation for the submitted work. The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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Epidemiology and aetiology of maternal bacterial and viral infections in low- and middle-income countries

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Background Maternal morbidity and mortality in low and middle income countries has remained exceedingly high. However, information on bacterial and viral maternal infections, which are important contributors to poor pregnancy outcomes, is sparse and poorly characterised. This review aims to describe the epidemiology and aetiology of bacterial and viral maternal infections in low and middle income countries.

Methods A systematic search of published literature was conducted and data on aetiology and epidemiology of maternal infections was extracted from relevant studies for analysis. Searches were conducted in parallel by two reviewers (using OVID) in the following databases: Medline (1950 to 2010), EMBASE (1980 to 2010) and Global Health (1973 to 2010).

Results Data from 158 relevant studies was used to characterise the epidemiology of the 10 most extensively reported maternal infections with the following median prevalence rates: *Treponema pallidum* (2.6%), *Neisseria gonorrhoeae* (1.5%), *Chlamydia trachomatis* (5.8%), Group B *Streptococcus* (8.6%), bacterial vaginosis (20.9%), hepatitis B virus (4.3%), hepatitis C virus (1.4%), *Cytomegalovirus* (95.7% past infection), *Rubella* (8.9% susceptible) and *Herpes simplex* (20.7%). Large variations in the prevalence of these infections between countries and regions were noted.

Conclusion This review confirms the suspected high prevalence of maternal bacterial and viral infections and identifies particular diseases and regions requiring urgent attention in public health policy planning, setting research priorities and donor funding towards reducing maternal morbidity and mortality in low and middle income countries.

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Maternal morbidity and mortality in low and middle income countries are still unacceptably high. It was estimated that 529 000 maternal deaths occurred throughout the world annually in 2000 (1). This estimate was recently updated with a figure of 273 500 deaths in 2011, the majority of which occurred in poor countries (2). The problem of maternal health has gained the attention of the global community, as exemplified by United

Nations Millennium Development Goal (MDG) 5, which is aimed at reducing the maternal mortality ratio by three quarters and ensuring universal access to reproductive healthcare by 2015 (3). With only 5 years left to achieve MDGs, progress towards the maternal health MDG has been one of the most disappointing, leading to its being highlighted as an urgent global priority at the September 2010 UN Summit on MDGs (4).

The disparity in maternal health between the developed and developing world can be attributed largely to poor access and quality of reproductive healthcare in developing countries (5). As a result, maternal mortality in developing countries remains high due to largely preventable causes such as haemorrhage, hypertensive disorders, abortion related complications and sepsis/infection (6).

An estimated 9.7% of maternal deaths in Africa are due to puerperal sepsis (6). Bacterial and viral infections during pregnancy contribute towards maternal morbidity and mortality and are associated with adverse pregnancy outcomes including spontaneous abortion, stillbirth, prematurity and low birth weight. Furthermore, some infections can be transmitted vertically to neonates, leading to subsequent neonatal morbidity and mortality (7). Most maternal infections can be diagnosed and treated during pregnancy, preventing morbidity and mortality of both mother and child. The reduction of maternal infections in the developing world is highly dependent on the effective use of limited health resources to diagnose and treat these infections.

The planning of effective public health measures is currently limited by the lack of information available on the precise epidemiology and aetiology of bacterial and viral maternal infections. Lack of information can also negatively impact donor interest and international commitment. This review aims to summarize published literature on the aetiology and epidemiology of bacterial and viral maternal infections in low and middle income countries. Additionally, the review aims to identify gaps in available information on the subject. This epidemiological information can subsequently be used to identify similarities and differences in the causes of maternal infection within and between geographic regions, and to guide local and international public health initiatives to reduce the prevalence and burden of these infections.

METHODS

Literature search terms

Initial searches were conducted to identify suitable keywords and MeSH headings to use in the final search (**Table 1**). The search strategy was prepared with input from a librarian. Searches were conducted in parallel by two reviewers (using OVID) in the following databases on 1 August 2010: Medline (1950 to August Week 4 2010), EMBASE (1980 to 2010 Week 30) and Global Health (1973 to August 2010).

Table 1 Search terms used to identify published articles on the prevalence and etiology of maternal infections in the developing world

exp Infection/
AND
exp Pregnancy/ OR exp Pregnancy Complications, Infectious/
AND
exp Developing Countries OR africa/ or africa, northern/ or algeria/ or egypt/ or libya/ or morocco/ or tunisia/ or "africa south of the sahara"/ or africa, central/ or cameroon/ or central african republic/ or chad/ or congo/ or "democratic republic of the congo"/ or gabon/ or africa, eastern/ or burundi/ or djibouti/ or eritrea/ or ethiopia/ or kenya/ or rwanda/ or somalia/ or sudan/ or tanzania/ or uganda/ or africa, southern/ or angola/ or botswana/ or lesotho/ or malawi/ or mozambique/ or namibia/ or south africa/ or swaziland/ or zambia/ or zimbabwe/ or africa, western/ or benin/ or burkina faso/ or cape verde/ or cote d'ivoire/ or gambia/ or ghana/ or guinea/ or guinea-bissau/ or liberia/ or mali/ or mauritania/ or niger/ or nigeria/ or senegal/ or sierra leone/ or togo/ or caribbean region/ or west indies/ or "antigua and barbuda"/ or cuba/ or dominica/ or dominican republic/ or grenada/ or guadeloupe/ or haiti/ or jamaica/ or martinique/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or central america/ or belize/ or costa rica/ or el salvador/ or guatemala/ or honduras/ or nicaragua/ or panama/ or latin america/ or mexico/ or south america/ or argentina/ or bolivia/ or brazil/ or chile/ or colombia/ or ecuador/ or french guiana/ or guyana/ or paraguay/ or peru/ or suriname/ or uruguay/ or venezuela/ or asia/ or asia, central/ or kazakhstan/ or kyrgyzstan/ or tajikistan/ or turkmenistan/ or uzbekistan/ or asia, southeastern/ or borneo/ or brunei/ or cambodia/ or east timor/ or indonesia/ or laos/ or malaysia/ or mekong valley/ or myanmar/ or philippines/ or thailand/ or vietnam/ or asia, western/ or bangladesh/ or bhutan/ or india/ or sikkim/ or middle east/ or afghanistan/ or iran/ or iraq/ or jordan/ or lebanon/ or syria/ or turkey/ or yemen/ or nepal/ or pakistan/ or sri lanka/ or far east/ or china/ or tibet/ or "democratic people's republic of korea"/ or mongolia/ or taiwan/ or atlantic islands/ or azores/ or albania/ or lithuania/ or bosnia-herzegovina/ or bulgaria/ or byelarus/ or "macedonia (republic)"/ or moldova/ or montenegro/ or romania/ or russia/ or bashkiria/ or dagestan/ or moscow/ or siberia/ or serbia/ or ukraine/ or yugoslavia/ or armenia/ or azerbaijan/ or "georgia (republic)"/ or indian ocean islands/ or comoros/ or madagascar/ or mauritius/ or reunion/ or seychelles/ or fiji/ or papua new guinea/ or vanuatu/ or guam/ or palau/ or "independent state of samoa"/ or tonga/

Study inclusion and exclusion criteria

Studies were screened by title and then by abstract for relevance. Studies were deemed relevant if they provided information on the aetiology or epidemiology of bacterial and viral infections in pregnant women in developing countries. These studies were then grouped according to pathogen studied, with some studies providing information on multiple pathogens. Studies providing information on the epidemiology of parasitic infections in pregnant women were identified but not analyzed, as they were addressed in a separate review. Studies reporting the prevalence of maternal HIV infection were identified but not included for analysis, as this information is available through other sources. Relevant English language papers were analyzed

in this work, along with the Chinese electronic databases, with the intention of translating and analyzing non-English papers, too. The inclusion criteria were:

Subjects: Pregnant women at any stage of pregnancy or labour, including the puerperium (up to 42 days after labour);

Study location: Low and middle income countries (as defined by The World Bank in 2010);

Study design and sampling methods: No restrictions applied;

Data collection: Only studies that provided evidence of bacterial or viral infection using microbiological or serological test results were included;

Results: Papers were selected if they provided information on the burden of a particular pathogen (the prevalence of a particular infection in pregnant women in the community over time/incidence) and/or the aetiology of bacterial and viral maternal infections (prevalence of a specific pathogen/infection).

Quality criteria

Only studies with more than 500 subjects were included, because we wanted to protect strongly against implausible proportional contributions of certain pathogens which could have occurred due to chance in smaller data series. Papers were required to describe their samples and methods in detail, and provide microbiological or serological evidence of the aetiology of infection.

Data extraction

Information on pathogen studied, sample population (pregnant women studied during pregnancy or at labour) and size, study setting, duration and type, microbiological/serological test used and results were extracted from abstracts and full papers for analysis.

Data analysis

Epidemiology and aetiology of bacterial and viral maternal infections were summarized according to the pathogen studied. Only pathogens with 5 or more studies reporting on its epidemiology and/or aetiology were analyzed. Median prevalence of each infection was calculated and trends in the prevalence of maternal infections were noted.

Selection of studies

The final search yielded 8580 relevant titles. **Figure 1** outlines the results of the search process and application of inclusion and exclusion criteria, resulting in the final panel of studies from which data was extracted.

Studies retained for data extraction (n=158) characterized the prevalence of 5 bacterial pathogens (*Treponema pallidum, Neisseria gonorrhoeae, Chlamydia trachomatis,* Group B *Streptococcus*, bacterial vaginosis) and 5 viral pathogens (hepatitis B virus, hepatitis C virus, *Cytomegalovirus, Rubella, Herpes simplex*) among pregnant women in developing countries, with three further reports providing secondary cross-sectional insights or reviews of the literature in this field which were considered useful (8–168). Studies reporting prevalence maternal HIV infection (n=167) were not included in the analysis.

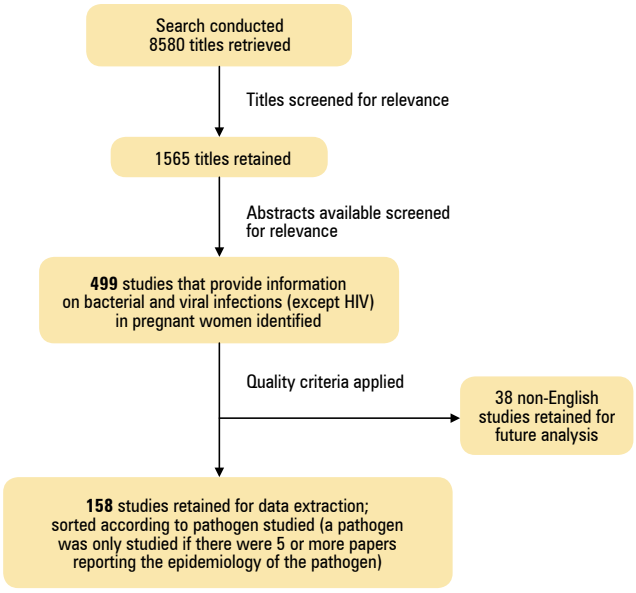

Figure 1 Summary of the literature search.

RESULTS

Prevalence of bacterial infections

Syphilis (Treponema pallidum). Seventy-two studies characterizing the prevalence of maternal syphilis in 36 developing countries were identified (**Supplementary Table 1**). The features and results of these studies are summarised in **Figures 2–5**.

In terms of study design, 58.3% of the identified studies were cross sectional, whilst 18.1% were screening studies. The majority of the studies (90.3%) were conducted in healthcare facilities (58.3% in antenatal or prenatal clinics), suggesting either awareness towards the need for antenatal screening for maternal syphilis infection, or merely that it is much easier to recruit study subjects in health care facilities. The remaining studies (5.6%) were community-based and the study setting was not specified in 4.2%.

Rapid Plasma Reagent (RPR) testing was used to detect antitreponemal antibodies in many studies (49%), often in combination with another test, most commonly the *Treponema*

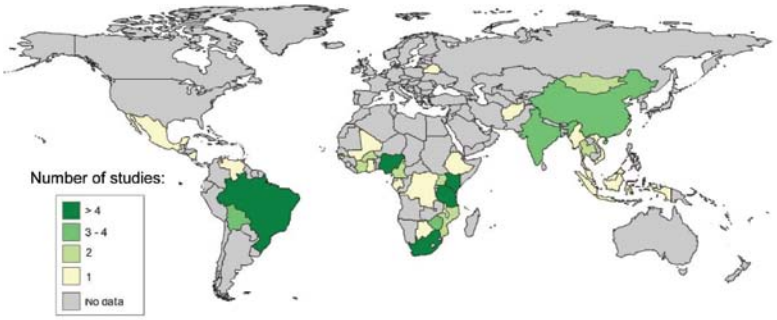

Figure 2 Geographical distribution of studies (n=72) reporting the prevalence of maternal syphilis; "no data" in the legend refers to low and middle-income countries only, as data from high-income countries were not the subject of this study.

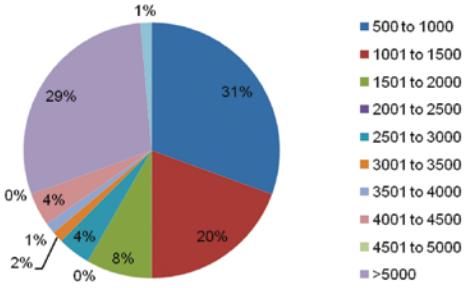

Figure 3 Distribution according to the size of population studied in 72 studies reporting maternal syphilis prevalence.

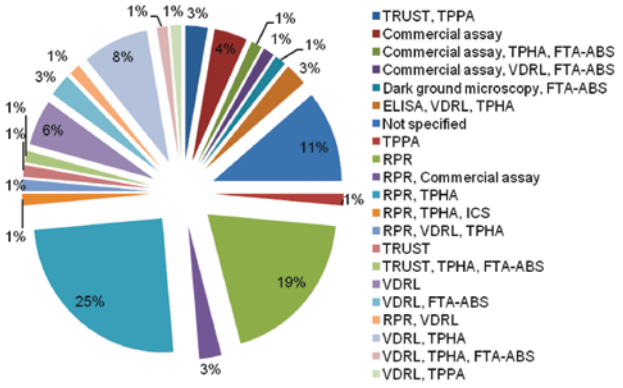

Figure 4 Techniques used to diagnose maternal syphilis in the 72 studies identified. TRUST – Toluidine red unheated serum test; TPPA – Treponema pallidum particle agglutination test; TPHA – Treponema pallidum haemagglutination test; FTA-ABS – Fluorescent treponemal antibody absorption; VDRL – Venereal Disease Research Laboratory test; RPR – Rapid Plasma Reagent; ICS – immunochromatographic strip.

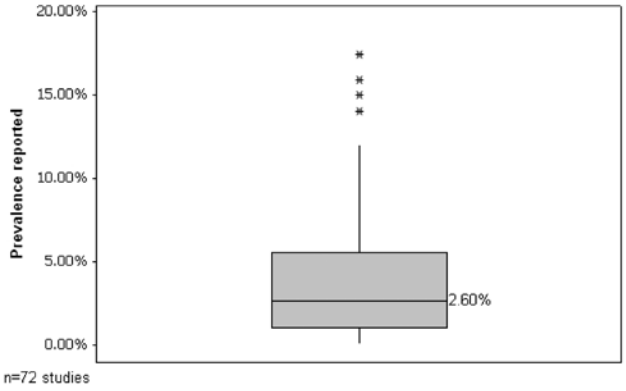

Figure 5 Box plot of syphilis prevalence reported by the 72 relevant studies. All studies measured prevalence by detecting the presence of antibodies to *Treponema pallidum*. The following number summaries are depicted in the boxplot: the smallest observation (sample minimum), lower quartile (25%), median (50%), upper quartile (75%), and largest observation (sample maximum). Asterisks indicate outliers.

pallidum Haemagglutination Assay (TPHA) (**Figure 4**). This is because RPR is cheap and simple to perform, but false positive results are common, necessitating confirmatory testing (7). Particularly high prevalence of maternal syphilis was reported in studies from Cameroon, South Africa and Zimbabwe (around 15.0%). Both studies from Cameroon were conducted in the Yaounde province, and show an increase in the prevalence of maternal syphilis from 15.9% in 1992 to 17.4% in 1998 (17,66,107,130).

Gonorrhoea (Neisseria gonorrhoeae). Twenty-one studies providing information of the prevalence of maternal *Neisseria gonorrhoeae* infection were identified (**Supplementary table 2**). The characteristics of these studies and the prevalence reported are summarized in the **Figures 6–9**.

With regards to study design, 20 studies (95.2%) were cross sectional and 1 was a randomized controlled trial (data from the control group was extracted). The majority of the studies (80.9%) were carried out in healthcare facilities and a minority was community-based (19.1%). Median prevalence of maternal gonococcal infection was relatively low, at 1.5% (**Figure 9**). However, higher prevalence of maternal gonococcal infection was reported in studies from Mongolia (6.1%), Vanuatu (5.9%) and Zimbabwe (5.8%) suggesting the need for targeted action in these countries (12,79,145).

Chlamydia trachomatis. Nineteen studies reporting the prevalence of maternal *Chlamydia trachomatis* (CT) infection were identified (**Table 2**).

These studies diagnosed maternal infection by detecting antibodies towards *C. trachomatis* or by pathogen detection in urine samples or endocervical swabs using PCR. The median prevalence of maternal *C. trachomatis* infection is 5.80%. Particularly high prevalence of maternal *C. tracho-*

Table 2 Characteristics and results of studies (n=19) reporting prevalence of maternal *Chlamydia trachomatis* infection

Article	Location, setting of study	Type, duration of study	Population	Results / Prevalence	Technique used
Msuya *et al*, 2009 (100)	Tanzania, 2 primary health clinics	Cross sectional study, 21 months	2654 pregnant women	17.5%	ELISA detecting anti-chlamydial IgG
Jalil *et al,* 2008 (63)	Brazil, prenatal services in 6 cities	Cross sectional study, 1 year	3003 pregnant women	CT prevalence of 9.4%	Hybrid capture technique
Kinoshita-Moleka *et al*, 2008 (70)	Democratic Republic of Congo, 2 maternity clinics	Cross sectional study, 4 months	529 pregnant women	1.7%	PCR
Lujan *et al,* 2008 (89)	Mozambique, antenatal clinic	Cross sectional study, 5 months	835 first void urine samples from pregnant women	4.1%	PCR
Romoren *et al*, 2007 (127)	Botswana, antenatal clinic	Cross sectional study, singular time point	703 pregnant antenatal care attendees	8% prevalence	LCR
Chen *et al*, 2006 (27)	China, antenatal clinic	Cross sectional study, 3 months	504 pregnant women	10.1%	PCR
Thammalangsy *et al*, 2006 (156)	Laos, 2 hospitals	Cross sectional study, 7 months	500 antenatal attendees	10.2% by nucleic acid hybridisation and 9.6% by PCR	Nucleic acid hybridisation, PCR
Amindavaa *et al*, 2005 (12)	Mongolia, prenatal clinics	Cross sectional survey, 11 months	2000 pregnant women	19.3%	PCR
Apea-Kubi *et al*, 2004 (14)	Ghana, gynaecology clinics at teaching hospital	Cross sectional study, singular time point	517 pregnant women	3% prevalence	RNA detection kit
Sullivan *et al*, 2003 (145)	Vanuatu, antenatal clinic	Cross sectional study, 12 months	547 pregnant women	21.5%	PCR
Gray *et al*, 2001 (53)	Uganda, community based	Randomised control trial, duration not specified	1576 pregnant women in the control arm of the study	2.7%	LCR
Mayank *et al*, 2001 (97)	India, community based	Cross sectional study, duration not specified	600 pregnant women	4.3%	ELISA
Latif *et al*, 1999 (79)	Zimbabwe, Antenatal and primary care clinics	Cross sectional study	1189 asymptomatic pregnant women	5.8% (and/or Gonococcal infection)	Not specified
Mulanga-Kabeya *et al*, 1999 (101)	Mali, community based	Cross sectional study, 1 month	549 pregnant women	5.0%	EIA
Bourgeois *et al*, 1998 (21)	Gabon, 3 antenatal clinics	Cross sectional study, 5 months	646 pregnant women	9.9%	EIA
Kilmarx *et al,* 1998 (69)	Thailand, antenatal clinics	Cross sectional study, singular time point	500 pregnant mothers in Chiang Rai, 521 pregnant mothers in Bangkok	5.70% prevalence	PCR
Diallo *et al*, 1997 (38)	Ivory Coast, antenatal clinic	Cross sectional study, 4 months	546 pregnant women	5.5%	Culture, EIA
Meda *et al*¸ 1997 (98)	Burkina Faso, 2 antenatal clinics	Cross sectional study, duration not specified	645 pregnant women	3.1%	EIA
Joesoef *et al*, 1996 (65)	Indonesia, prenatal clinic	Cross sectional study, 15 months	599 pregnant women	8.2%	Direct immuno-fluorescence

EIA – enzyme immunoassay, ELISA – enzyme-linked immunosorbent assay, LCR – ligase chain reaction, PCR – polymerase chain reaction

Table 3 Characteristics and results of studies (n=12) reporting prevalence of maternal Group B *Streptococcus* (GBS) colonisation

Article	Location, setting of study	Type, duration of study	Population	Results / Prevalence	Technique used
Seoud *et al*, 2010 (134)	Lebanon, 3 hospitals	Cross sectional study, 8 months	775 pregnant mothers	17.7% positive for GBS colonisation	Not specified
Mavenyengwa *et al*, 2010 (96)	Zimbabwe, 3 communities	Cohort study, duration not specified	780 women (one or more samples collected)	60.3% positive for GBS colonisation	Culture
Mansouri *et al*, 2008 (94)	Iran, 3 major non-private hospitals	Cross sectional study, 11 months	602 pregnant women at childbirth	9.1% were colonised by GBS	Culture
Namavar *et al,* 2008 (105)	Iran, hospital	Cross sectional study, 6 months	1197 pregnant women at labour	9.1% had rectovaginal colonisation with GBS	Culture
Zusman *et al*, 2006 (168)	Brazil, 2 hospitals	Prospective study, 5 months	598 pregnant women	17.9% maternal colonisation rate	Culture
Goto *et al*, 2005 (52)	Vietnam, community based	Survey, duration not specified	505 pregnant women	4%	Culture
Larcher *et al*, 2005 (78)	Argentina, hospital	Prospective study, 18 months	1228 pregnant women	1.4% maternal colonisation rate	Culture
Sidky & Thomas, 2002 (139)	UAE, hospital	Cross sectional study, 2 months	891 pregnant women at delivery	21.5% maternal colonisation rate	Culture
Toresani *et al*, 2001 (158)	Argentina, hospital	Cross sectional study, 25 months	531 pregnant women	3.2% were positive for GBS	Culture
Werawatakul *et al*, 2001 (164)	Thailand, hospital	Cross sectional study, 5 months	902 pregnant women presenting at labour	6.2% maternal colonisation rate	Culture
Ocampo-Torres *et al*, 2000 (111)	Mexico, 3 public hospitals	Cross sectional study, 8 months	910 pregnant women at delivery	8.6% GBS colonisation rate	Culture, Latex agglutination
Olanisebe & Adetosoye, 1986 (113)	Nigeria, 4 government hospitals	Cross sectional study, duration not specified	500 pregnant women (2^{nd} and 3^{rd} trimester)	1.6% positive for GBS	Culture

UAE – United Arab Emirates

Figure 6 Geographical distribution of studies (n=21) reporting prevalence of maternal gonococcal infection; "no data" in the legend refers to low- and middle-income countries only, as data from high-income countries were not the subject of this study.

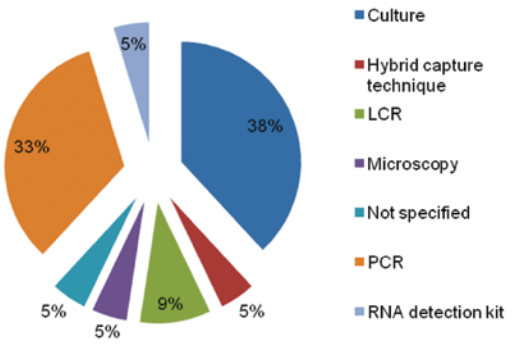

Figure 7 Techniques used to identify gonococcal infection in the 21 studies identified (LCR – ligase chain reaction).

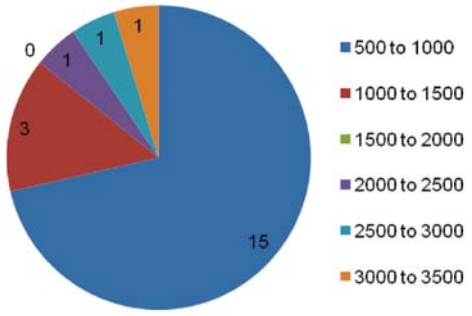

Figure 8 Size of study populations in 21 studies identified reporting maternal gonococcal infection prevalence.

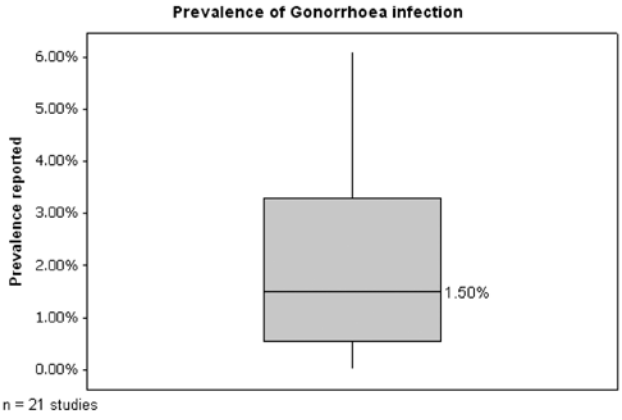

Figure 9 Prevalence of *N. gonorrhoeae* detected in relevant studies (n=21). All studies measured prevalence by detecting the infecting organism in pregnant women. The following number summaries are depicted in the boxplot: the smallest observation (sample minimum), lower quartile (25%), median (50%), upper quartile (75%), and largest observation (sample maximum).

matis infection was identified in Vanuatu (21.5%), Mongolia (19.3%) and Tanzania (17.5%) (12,100,145).

Group B Streptococcus. Twelve studies reporting the prevalence of maternal Group B *Streptococcus* (GBS) (*S. agalactiae)* colonisation were identified (**Table 3**).

The majority of studies diagnosed GBS colonization by direct culture of vaginal swabs. Median prevalence of maternal GBS colonization was 8.85%. The highest prevalence of maternal GBS colonization reported was 60.3% in 3 communities across Zimbabwe, which was significantly higher than the prevalence reported by other studies. However this prevalence was reported as not significantly associated with adverse perinatal outcomes (96). Higher prevalence was also noted in Lebanon and the United Arab Emirates (136,139).

Bacterial vaginosis. Eleven studies reported the prevalence of bacterial vaginosis (**Table 4**).

The median prevalence of maternal bacterial vaginosis was 20.9%. Especially high prevalence was reported in Uganda, Botswana and Zimbabwe, highlighting high prevalence of bacterial vaginosis in sub-Saharan Africa. The majority of studies used microscopy of vaginal wet mounts in combination with established criteria for diagnosing bacterial vaginosis (53,75,126).

Prevalence of Viral Pathogens

Hepatitis B virus. Thirty-nine studies characterizing the prevalence of maternal Hepatitis B infection were identified (**Supplementary Table 3**), and their features and results are summarized in **Figures 10–13**.

The majority of identified studies were conducted in a healthcare facility (87.2%) whilst 5.1% were community based and 7.7% of studies did not specify the setting. Most of the studies were also cross sectional (69.2%) in nature, with remaining studies being retrospective observational

Table 4 Characteristics and results of studies (n=11) reporting prevalence of bacterial vaginosis in pregnant women

Article	Location, setting of study	Type, duration of study	Population	Results / Prevalence	Technique used
Kurewa *et al*, 2010 (75)	Zimbabwe, peri-urban clinics	Cross sectional study, 19 months	691 pregnant women	32.6%	Amsel's criteria
Msuya *et al*, 2009 (100)	Tanzania, 2 primary health clinics	Cross sectional study, 21 months	2654 pregnant women	20.9%	Amsel's criteria
Kirakoya-Samadoulougou *et al*, 2008 (71)	Burkina Faso, 4 primary health centres	Cross sectional study, 3 months	2133 pregnant women with analysable data	6.4%	Nugent scoring method
Romoren *et al*, 2007 (127)	Botswana, multiple antenatal clinics	Cross sectional study, 5 months	703 pregnant women	38.0%	Microscopy
Azargoon & Darvishzadeh, 2006 (16)	Iran, hospital	Cohort study, duration not specified	1223 pregnant women	16.0%	Vaginal pH, saline wet mount, Amsel tests
Thammalangsy *et al*, 2006 (156)	Laos, 2 hospitals	Cross sectional study, 7 months	500 pregnant antenatal attendees	14.4% by Amsel's criteria and 22.0% by Nugent's score	Amsel's criteria, Nugent's score
Goto *et al*, 2005 (52)	Vietnam, community based	Survey, duration not specified	505 pregnant women in 10 communes	7%	Nugent criteria
Gray *et al*, 2001 (53)	Uganda, community based	Randomised control trial, duration not specified	1576 pregnant women in the control arm of the study	48.5%	Microscopy
Mayank *et al*, 2001 (97)	India, community based	Cross sectional study, duration not specified	600 pregnant women	18%	Microscopy
Taha *et al*, 1999 (150)	Malawi, hospital	Cross sectional study, 25 months	9126 pregnant women	30%	Vaginal wet mounts
Meda *et al*, 1997 (98)	Burkina Faso, 2 antenatal clinics	Cross sectional study, duration not specified	645 pregnant women	13%	Microscopy

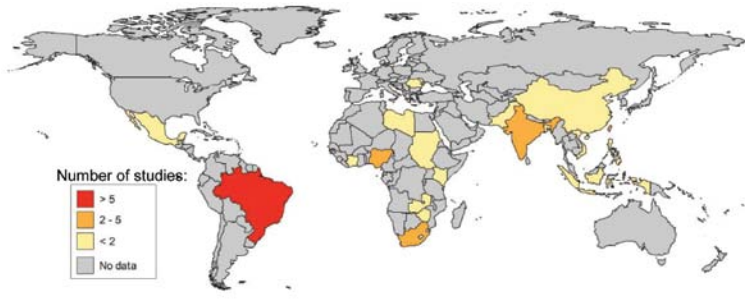

Figure 10 Geographical distribution of studies (n=39) providing information on prevalence of maternal hepatitis B virus (HBV) infection; "no data" in the legend refers to low and middle-income countries only, as data from high-income countries were not the subject of this study.

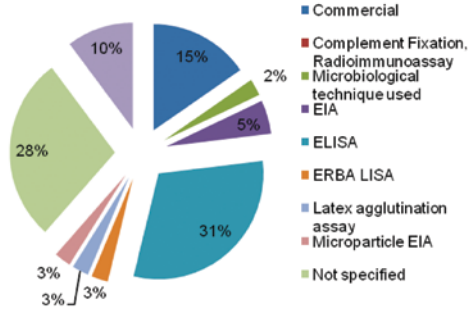

Figure 11 Techniques used to identify hepatitis B virus (HBV) infection in 39 studies.

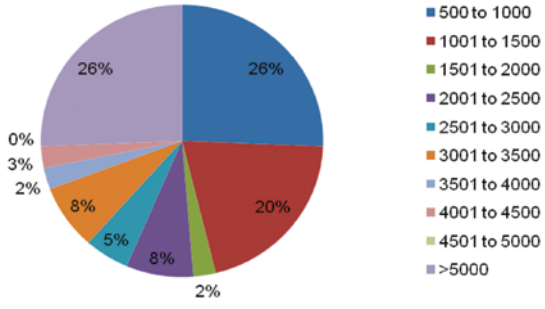

Figure 12 Sizes of study populations in 39 studies reporting maternal hepatitis B virus (HBV) infection prevalence.

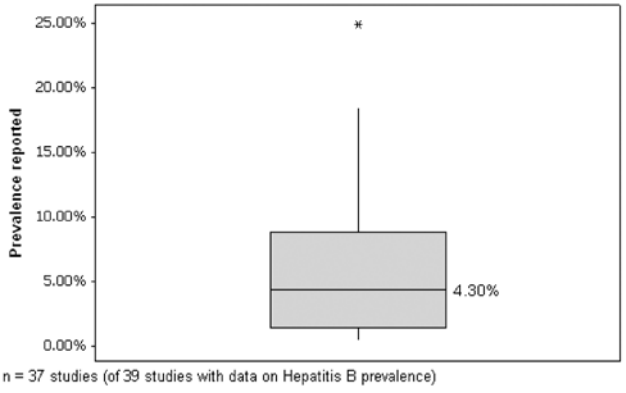

Figure 13 Box plot showing prevalence of hepatitis B virus (HBV) infection detected in relevant studies (n=37). Only 30 of 37 relevant studies measured prevalence by detecting hepatitis B surface antigen (HBsAg) in pregnant women. The following number summaries are depicted in the boxplot: the smallest observation (sample minimum), lower quartile (25%), median (50%), upper quartile (75%), and largest observation (sample maximum). Asterisk indicates an outliner.

(17.9%), surveys (5.1%) and either prospective, cohort or case control studies (2.5% each).

The majority of studies screened for the presence of maternal HBV infection by detecting Hepatitis B surface antigen (HBsAg) in maternal serum. Particularly high maternal HBV prevalence (25%) was identified in Zimbabwe (90), Brazil (20) and Taiwan (83).

Hepatitis C virus. Twenty-one studies reporting the prevalence of maternal Hepatitis C virus (HCV) infection were identified (**Supplementary Table 4**). The features and findings of these studies are summarized in **Figures 14 to 17**.

Almost all studies reporting maternal HCV prevalence were conducted in healthcare facilities (95.2%) and one did not specify the study setting. The majority of studies were also cross sectional (80.9%), with the remaining studies being case control studies (14.3%), prospective studies (9.5%) and one serological survey (4.8%).

Median maternal exposure to HCV (anti-HCV) prevalence reported was 1.4%. Active infection prevalence (HCV RNA) was reported in 6 studies and median active HCV infection prevalence from these studies was 1.2%. Two studies from Egypt reported especially high prevalence of maternal HCV exposure (15.8% and 15.7%) and active infection rates (10.8% and 10.9%), highlighting a local problem with maternal HCV infection in Egypt (136,143).

Rubella virus. Fifteen studies characterizing the epidemiology of maternal rubella were identified (**Table 5**).

These studies detected the presence of maternal anti-rubella IgG as a marker of past infection or immunization and mothers who did not possess these antibodies were susceptible to rubella infection. Maternal IgM was detected in some studies as a marker of recent or current infection, which is associated with an increased risk of vertical transmission. Median maternal susceptibility to rubella was

Table 5 Characteristics and results of studies (n=15) reporting prevalence of maternal rubella infection

Article	Location, setting of study	Type, duration of study	Population	Results / Prevalence	Technique used
Lin *et al*, 2010 (86)	Taiwan, hospital	Cross sectional study, 7 years	10,089 pregnant women	Seronegativity was 14.0%	Microparticle EIA
Tamer *et al*, 2009 (152)	Turkey, antenatal clinic	Cross sectional study, duration not specified	1972 serum samples from pregnant women	Seropositivity for anti-rubella IgG, IgM and IgG+IgM together was 96.1%, 0.2% and 1.8%, respectively	Commercial ELISA (detecting IgG and IgM)
Ai & Ee, 2008 (8)	Malaysia, antenatal clinics and hospital	Cross sectional study, duration not specified	500 pregnant mothers	11.4% were susceptible to Rubella	Rubella IgG studies
Majlessi *et al*, 2008 (92)	Iran, health centres	Cross sectional study, 2 years	965 pregnant women	Estimated rubella immunity rate was 91.1%, Nonimmunity rate was 8.9%	ELISA
Das *et al*, 2007 (34)	India, hospital	Screening, duration not specified	1115 pregnant women with bad obstetric history, 500 normal pregnant women	3.6% seropositivity (*BOH), 0% seropositivity (normal)	ELISA (Detecting IgM)
Ocak *et al*, 2007 (110)	Turkey, antenatal clinic	Retrospective observational, 23 months	1652 pregnant women	Anti-rubella IgG and IgM antibodies were reactive in 95.0%, and in 0.54%	ELISA (detecting IgG and IgM)
Pehlivan *et al*, 2007 (119)	Turkey, community based	Cross sectional study, 7 months	824 women from 60 clusters; 803 eligible for serological study	93.8% positive for anti-rubella IgG, 0.6% were IgM and IgG positive, 5.6% were susceptible	Micro ELISA (detecting IgG and IgM)
Tseng *et al*, 2006 (160)	Taiwan, hospital	Retrospective observational, 4 years	5007 pregnant women	13.4% susceptible among Taiwanese women; 29.1% susceptible among non-Taiwanese women	Microparticle EIA
Barreto *et al*, 2006 (18)	Mozambique, antenatal clinics	Cross sectional serosurvey, 3 months	974 pregnant women at antenatal clinic attendance	95.3% positive for Rubella IgG	ELISA
Corcoran & Hardie, 2006 (31)	South Africa, antenatal clinics	Cross sectional study, duration not specified	1200 serum samples from a 2003 HIV/syphilis survey	96.5% immune	ELISA
Desinor *et al*, 2004 (36)	Haiti, hospital	Cross sectional study, 4 months	503 pregnant women; 8 excluded leaving 495	95.2% were seropositive	EIA
Weerasekera *et al*, 2003 (163)	Sri Lanka, antenatal clinic	Cross sectional study, 2 years	500 maternal blood samples, before 16th week of gestation	82% were positive for rubella specific IgG, 75% gave a history of vaccination against rubella before their present pregnancy	ELISA (detecting IgG and IgM)
Palihawadana *et al*, 2003 (116)	Sri Lanka, multiple antenatal clinics	Cross sectional study, duration not specified	620 pregnant women	76% of pregnant females were seropositive	ELISA (detecting IgG)
Ashrafunnessa Khatun, *et al*, 2000 (15)	Bangladesh, hospital	Cross sectional study, 11 months	609 pregnant women	85.9% were seropositive and 14.1% were seronegative	ELISA
Dos Santos *et al*, 2005 (39)	Brazil, prenatal testing	Cross sectional study, 8 months	1024 pregnant women	77.4%	Haemagglutinin Inhibition Assay

EIA – enzyme immunoassay, ELISA – enzyme-linked immunosorbent assay

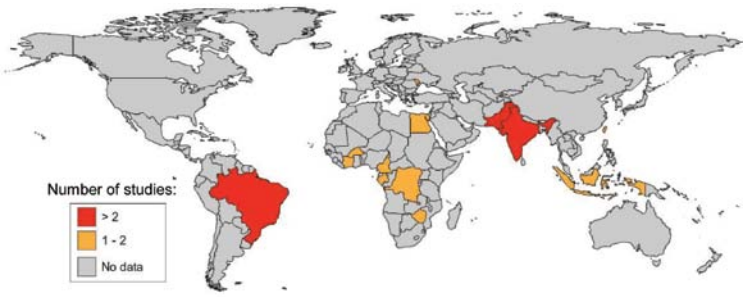

Figure 14 Geographical distribution of studies (n=21) providing reporting prevalence of maternal hepatitis C (HCV) infection; "no data" in the legend refers to low and middle-income countries only, as data from high-income countries were not the subject of this study.

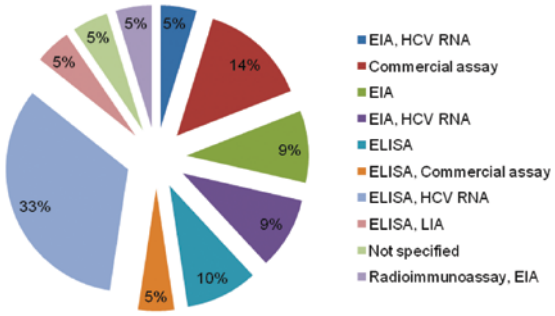

Figure 15 Techniques used to diagnose maternal hepatitis C (HCV) infection (n=21 studies); HCV RNA refers to tests detecting HCV RNA, including PCR and RT-PCR.

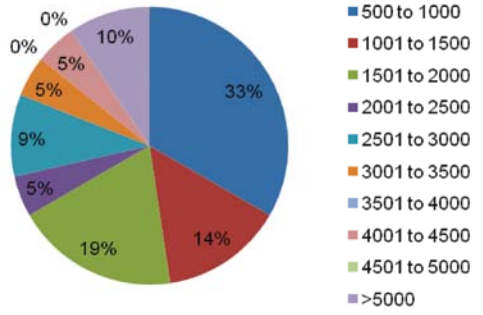

Figure 16 Size of study populations of 21 studies reporting maternal hepatitis C (HCV) infection prevalence.

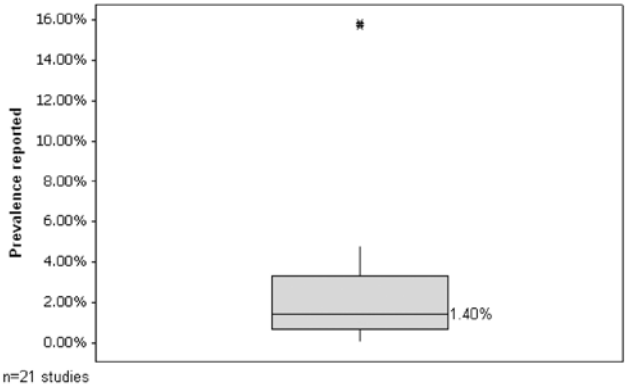

Figure 17 Box plot showing prevalence of hepatitis C virus (HCV) exposure detected in relevant studies (n=21). All studies diagnosed the history of HCV infection by detecting anti-HCV antibodies in serum. The following number summaries are depicted in the boxplot: the smallest observation (sample minimum), lower quartile (25%), median (50%), upper quartile (75%), and largest observation (sample maximum). Asterisk indicates an outlier.

8.9%. Higher susceptibility rates were reported in Sri Lanka, Brazil and Taiwan (2 studies) (39,84,160,163).

Cytomegalovirus. Five studies on maternal cytomegalovirus (CMV) infection prevalence were identified (**Table 6**).

The median prevalence of maternal IgG to CMV (calculated from 4 studies that reported this) was 95.7%, indicating a high proportion of mothers with previous exposure to CMV. One hospital-based study in India identified a statistically significant higher prevalence of CMV IgM (indicating active or recent infection) in mothers with Bad Obstetric History (BOH), highlighting a role for maternal CMV infection in adverse pregnancy outcome in this setting (34).

Herpes simplex virus. Five studies outlining the prevalence of maternal Herpes simplex virus 2 (HSV-2) were identified (**Table 7**).

These studies detected the presence of antibodies to HSV as a marker of maternal infection. Median prevalence of HSV-2 was 20.7%. Higher seroprevalences were noted in Zimbabwe, Vanuatu and Tanzania (56,75,166).

DISCUSSION

Prevalence of bacterial and viral maternal infections

Our search of published literature relevant to the aetiology and epidemiology of bacterial and viral maternal infections in the developing world retrieved 499 titles. Analysis of these titles yielded 158 studies which provided detailed epidemiological information on 10 maternal infections. The 5 bacterial and 5 viral maternal infections identified in this panel represent maternal infections that were most extensively studied, suggesting that these infections have a high burden on pregnancy outcomes in the developing world. These infections also have potential adverse effects on neonates.

Our review confirms the suspected high prevalence of bacterial and viral maternal infections in the developing world, as demonstrated by the median prevalence rates calculated for each pathogen studied. Of particular concern are the

Table 6 Characteristics and results of studies (n=5) reporting prevalence of maternal cytomegalovirus (CMV) infection

Article	Location, setting of study	Type, duration of study	Population	Results / Prevalence	Technique used
Tabatabaee *et al*, 2009 (149)	Iran, hospital	Cross sectional study, 7 months	1472 pregnant women presenting at labour	97.69% seropositivity, 2.31% seronegativity; prevalence of active infection – 4.35%	Not specified
Das *et al*, 2007 (34)	India, hospital	Cross sectional study	1115 pregnant women with Bad obstetric history, 500 normal pregnant women	11% prevalence in women with Bad obstetric history, 4% prevalence in normal pregnant women	Commercial ELISA kit detecting anti-CMV IgM
Ocak *et al*, 2007 (110)	Turkey, hospital	Retrospective observational study, 2 years	1652 pregnant women	94.9%seropositivity for anti-CMV IgG, 0.4%positive for anti-CMV IgM	ELISA detecting anti-CMV IgG and IgM
Suarez *et al*, 1994 (144)	Chile, public outpatient department and a special clinic for university students	Cross sectional study, 3 years	939 pregnant women of a low socioeconomic level, and 123 pregnant university students	95% in low socioeconomic class; 69.9% in pregnant students; 2 primary infections occurred (1 in each group)	ELISA; initially seronegative women were tested again during 2nd and 3rd trimester to identify primary infections
Tamer *et al*, 2009 (152)	Turkey, antenatal clinics	Cross sectional study, singular time point	1972 samples of sera from pregnant women	Seroprevalence of anti-CMV IgG, IgM and IgG+IgM together were found in 96.4%, 0.7% and 1.9% of the pregnant women, respectively	Commercial ELISA kit

ELISA – enzyme-linked immunosorbent assay

Table 7 Characteristics and results of studies (n=5) reporting prevalence of maternal Herpes simplex virus (HSV) infection

Article	Location, setting of study	Type, duration of study	Population	Results / Prevalence	Technique used
Kurewa *et al*, 2010 (75)	Zimbabwe, peri-urban clinics	Cross sectional study, 19 months	691 pregnant women	51.10% seropositive	ELISA detecting IgG
Yahya-Malima *et al*, 2008 (166)	Tanzania, antenatal clinics (6)	Cross sectional study, duration not specified	1296 sera collected from pregnant women	20.7% prevalence of genital herpes	ELISA
Chen *et al*, 2007 (28)	China, antenatal clinic	Cross sectional study, 3 months	502 pregnant women	10.8% seroprevalence of HSV-2	Commer-cial ELISA to detect IgG
Haddow *et al*, 2007 (56)	Vanuatu, antenatal clinic	Cross sectional study, 1 to 2 years	535 pregnant women	32% seroprevalence of HSV-2	ELISA
Joesoef *et al*, 1996 (65)	Indonesia, prenatal clinic	Cross sectional study, 15 months	599 pregnant women	9.9% seroprevalence of HSV-2	Immuno-blot

ELISA – enzyme-linked immunosorbent assay

high prevalence rates of maternal syphilis (2.6%), *C. trachomatis* (5.8%), bacterial vaginosis (20.9%), hepatitis B virus (4.3%) and *Herpes simplex* virus (20.7%).

The prevalence of these infections also showed significant variance between countries and regions. The prevalence of maternal infections in sub-Saharan Africa is especially high, specifically in Zimbabwe (75,79,96,130), Tanzania (101, 166) and Cameroon (66,107). Previous studies have shown that all-cause obstetric risk and maternal mortality ratio are highest in Sub-Saharan Africa (1). The high prevalence of maternal infections in this region may have an important contributory role towards the high maternal morbidity and mortality seen in Sub-Saharan Africa. Regional differences in the prevalence of maternal infections are likely to be closely related to the quality of reproductive healthcare available in different regions, or unique local scenarios.

Gaps in existing knowledge

In the process of reviewing the subject, we identified several facility-based retrospective studies reporting causes of maternal mortality. Many of these studies attributed a proportion of deaths to infection or sepsis, but were unable to provide microbiological or serological evidence of the specific aetiology of infection. Thus, these studies had to be excluded from the final panel of studies that we reviewed. This highlights a gap in existing knowledge on the epidemiology and impact of maternal infection, especially on the aetiology of infectious agents that lead to puerperal sepsis and subsequent mortality. Increased surveillance and diagnostic capabilities in healthcare facilities and in the community is needed to identify the aetiological agents responsible for puerperal sepsis and maternal mortality.

The prevalence of maternal infection reported by the studies identified in this review may be an underestimate of actual rates of infection as not all pregnant women in developing countries may have access to or choose to access formalized antenatal care. This could be due to financial constraints, difficulties in accessing these facilities and personal or cultural beliefs. In addition, antenatal care services may not have the capacity to routinely screen for maternal infections, especially those that are asymptomatic (such as *N. gonorrhoeae* and *C. trachomatis*) and those that require serological tests such as PCR and ELISA to diagnose (Hep-

atitis B and C), due to limited resources or expertise. These infrastructural problems are essential contributors to the persistence of high maternal morbidity and mortality in developing countries and need to be overcome in order to accurately characterize the burden of maternal infections in these countries.

Strengths and limitations

This is one of the first reviews to summarise the epidemiology of bacterial and viral maternal infections in the developing world (7). The search strategy devised is sensitive and specific, which allowed for a comprehensive review of available literature on this topic. The information generated in this review can be utilised to guide public health policy and the allocation of resources within local governments and by the international community towards improving maternal health. Limitations of this work include the exclusion of studies with less than 500 participants and the omission of pathogens with less than 5 papers reporting their prevalence. This was done to minimise the potential confounding effect that smaller, underpowered studies may have had on the overall prevalences reported and to increase the statistical robustness of the data presented.

This study could be further improved by analysing smaller studies that were identified and performing a sensitivity analysis of their results prior to inclusion. Also, it is likely that further valuable insights may be obtained from non-English articles of studies conducted in francophone parts of Africa (in French), South America (in Spanish) and in China (in Chinese), which could be accessed from appropriate databases. Reviewing non-English articles may assist in defining the epidemiology of pathogens for which we managed to identify few (<5) studies, as well as providing more robust data on the pathogens presented in this review. In addition, searching grey (unpublished) literature or contacting health officials and researchers in the field may also yield more country specific data on the subject, thus enabling more targeted and context-specific public health measures.

Recommendations and future work

Reducing the prevalence of maternal infections, and consequently maternal and neonatal morbidity and mortality, requires a concerted, multifaceted approach. Improvements in the provision, accessibility and uptake of antenatal care services are absolutely essential to reduce the prevalence of not only maternal infection but also other causes of maternal morbidity and mortality. This entails an improvement in antenatal booking, the number of antenatal visits and childbearing with professional assistance (40). Wherever possible, routine screening and treatment for maternal infections should be conducted. Alternatives to antenatal screening include syndromic management or risk assessment based approaches to treat maternal infection. Routine immunisation against vaccine-preventable diseases should also be implemented to reduce the eventual burden that these infections may have on pregnancy outcomes and neonates (7,132).

We hope that the gaps in information highlighted in this study will guide the design and implementation of studies to accurately assess the epidemiology of maternal infections in the developing world, especially in countries where the prevalence of maternal infection is unreported. Ideally, studies should be large, community-based and longitudinal, and investigate the association between pregnancy outcome and microbiological and serological evidence of maternal infection to accurately define the burden of maternal infections and their impact on pregnancy outcome (132). There is also a great need for the design of rapid point-of-care diagnostic tests for use in the field for the diagnosis of maternal infections. Affordable and novel therapeutics and interventions will also be beneficial in reducing the impact of maternal infections. These measures are dependent upon the co-operation of the research community and the altruism of industry to succeed.

More than US$ 40 billion (€ 30 billion) has been pledged towards the newly formed Global Strategy for Women's and Children's Health (169). These funds should be spent prudently on effective and sustainable measures to improve maternal health. The majority of this allocation should go towards the strengthening of basic antenatal care systems in developing countries. Because serious maternal infections are a major contributor to maternal morbidity and mortality, the early detection and treatment of infections is an important component of prenatal care. The continued support of the global community is also needed to ensure the improvement of maternal health in the developing world.

CONCLUSION

This review highlights the high bacterial and viral maternal infection rates in the developing world. Urgent, concerted action is required to reduce the burden of these infections. In addition to raising awareness about the severity of the problem of maternal infections in the developing world, data from this review will be beneficial in guiding public health policy, research interests and donor funding towards achieving MDG 5.

Acknowledgements: We thank Sheila Fisken, librarian, for her advice on databases and refining of search terms, and Edinburgh medical students Alasdair Campbell and Rachel McKinnon for their consultation on various aspects of the project.

Funding: Bill and Melinda Gates Foundation.

Ethical approval: Not required.

Authorship declaration: All authors designed and conducted the study and contributed to writing the paper.

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 support from Bill and Melinda Gates Foundation for the submitted work. The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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Epidemiology and aetiology of maternal parasitic infections in low- and middle-income countries

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Background There have been very few systematic reviews looking at maternal infections in the developing world, even though cutting maternal mortality by three quarters is United Nation's Millennium Development Goal number five. This systematic review has two aims. The first is to present the prevalence of parasitic infections in the developing world over the last 30 years and the second is to evaluate the quality and distribution of research in this field.

Methods A systematic review of Medline, EMBASE and Global Health databases was undertaken using pre-determined search criteria. Three levels of quality criteria for exclusion of inadequate studies identified 115 out of initial 8580 titles. The data were extracted for 5 domains: worldwide pathogen prevalence, year of study, study setting, sample size and diagnostic test for each pathogen.

Results The initial search retrieved 8580 results. From these titles, 43 studies on malaria, 12 studies on helminths, 49 studies on *Toxoplasma gondii*, 7 studies on Chagas disease, 5 studies on *Trichomonas*, 1 leishmaniasis study and 1 study on trichinellosis were extracted for analysis. High prevalence of malaria was found in Gabon (up to 57%) India (55%), Cameroon (50%), Yemen (55%), Nigeria (up to 64%) and Ghana (54%). High prevalence of hookworm infections was found in Nepal at 78.8% and high values of *Ascaris lumbricoides* were found in Nepal, (56.2%), Kenya (52.3%) and Gabon (45.5%). High levels of *Schistosoma mansoni* were found in Zimbabwe (50%) and Tanzania (63.5%). The prevalence of active *Toxoplasma gondii* infection was found to be highest in India (27.7%).

Conclusion This study highlights the large burden of maternal parasitic infections globally. It may serve as a useful starting point for health policy development and research prioritization in this area.

With 5 years to go until 2015 and the end of the period to achieve Millennium Development Goals (MDGs) targets, it is debatable how many of the MDGs will reach the aims defined in 2000. MDG 5 aims to: "Reduce by three quarters the maternal mortality ratio" (1). However, between

1990 and 2005, in Sub-Saharan Africa especially, little progress had been made and in some countries the figures have even increased (1). In 1990, the Democratic Republic of Congo had a maternal mortality ratio (MMR) of 870 per 100 000 and by 2005 it had increased to 1100 per 100 000 (1). In addition, in Tanzania, which is a more stable sub-Saharan African country, the MMR also increased from 770 per 100 000 in 1990 to 970 per 100 000 (1). At the recent review of the MDGs in 2010, the UN managed to secure US$ 40 billion (€ 30 billion) for women's and children's health alone (2).

Maternal deaths are due to many causes including haemorrhage, hypertensive disorders, abortion related complications, infections and sepsis (3). Maternal infections contribute to about 10–20% of these deaths (3). It is therefore imperative that there is up to date research on these topics. So far, there have been no systematic reviews of the data.

This review aims to summarise the research that has been undertaken in the past 30 years. It will look at the global distribution of research and the year in which the research was done. It will also look at how this research was undertaken, where the research was done, how many subjects were included in papers and what microbiological diagnostic methods were used. Finally the paper will set out an up-to-date picture of the prevalence of parasitic infections in the developing world over the last 30 years.

METHODS

Literature search terms

Initial searches were conducted to identify suitable keywords and MeSH headings to use in the final search (**Table 1**). The search strategy was prepared with an input from a librarian. Searches were conducted in parallel by two reviewers (using OVID) in the following databases on 1 August 2010: Medline (1950 to August Week 4 2010); EMBASE (1980 to 2010 Week 30) and Global Health (1973 to August 2010).

Table 1 Search terms used to identify published articles on the prevalence and aetiology of maternal infections in the developing world

exp Infection/
AND
exp Pregnancy/ OR exp Pregnancy Complications, Infectious/
AND
exp Developing Countries OR africa/ or africa, northern/ or algeria/ or egypt/ or libya/ or morocco/ or tunisia/ or "africa south of the sahara"/ or africa, central/ or cameroon/ or central african republic/ or chad/ or congo/ or "democratic republic of the congo"/ or gabon/ or africa, eastern/ or burundi/ or djibouti/ or eritrea/ or ethiopia/ or kenya/ or rwanda/ or somalia/ or sudan/ or tanzania/ or uganda/ or africa, southern/ or angola/ or botswana/ or lesotho/ or malawi/ or mozambique/ or namibia/ or south africa/ or swaziland/ or zambia/ or zimbabwe/ or africa, western/ or benin/ or burkina faso/ or cape verde/ or cote d'ivoire/ or gambia/ or ghana/ or guinea/ or guinea-bissau/ or liberia/ or mali/ or mauritania/ or niger/ or nigeria/ or senegal/ or sierra leone/ or togo/ or caribbean region/ or west indies/ or "antigua and barbuda"/ or cuba/ or dominica/ or dominican republic/ or grenada/ or guadeloupe/ or haiti/ or jamaica/ or martinique/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or central america/ or belize/ or costa rica/ or el salvador/ or guatemala/ or honduras/ or nicaragua/ or panama/ or latin america/ or mexico/ or south america/ or argentina/ or bolivia/ or brazil/ or chile/ or colombia/ or ecuador/ or french guiana/ or guyana/ or paraguay/ or peru/ or suriname/ or uruguay/ or venezuela/ or asia/ or asia, central/ or kazakhstan/ or kyrgyzstan/ or tajikistan/ or turkmenistan/ or uzbekistan/ or asia, southeastern/ or borneo/ or brunei/ or cambodia/ or east timor/ or indonesia/ or laos/ or malaysia/ or mekong valley/ or myanmar/ or philippines/ or thailand/ or vietnam/ or asia, western/ or bangladesh/ or bhutan/ or india/ or sikkim/ or middle east/ or afghanistan/ or iran/ or iraq/ or jordan/ or lebanon/ or syria/ or turkey/ or yemen/ or nepal/ or pakistan/ or sri lanka/ or far east/ or china/ or tibet/ or "democratic people's republic of korea"/ or mongolia/ or taiwan/ or atlantic islands/ or azores/ or albania/ or lithuania/ or bosnia-herzegovina / or bulgaria/ or byelarus/ or "macedonia (republic)"/ or moldova/ or montenegro/ or romania/ or russia/ or bashkiria/ or dagestan/ or moscow/ or siberia/ or serbia/ or ukraine/ or yugoslavia/ or armenia/ or azerbaijan/ or "georgia (republic)"/ or indian ocean islands/ or comoros/ or madagascar/ or mauritius/ or reunion/ or seychelles/ or fiji/ or papua new guinea/ or vanuatu/ or guam/ or palau/ or "independent state of samoa"/ or tonga/

Study inclusion and exclusion criteria

Studies were screened by title and then by abstract for relevance. Studies were deemed relevant if they provided information on the aetiology or epidemiology of parasitic infections in pregnant women in developing countries. These studies were then grouped according to pathogen studied, with some studies providing information on multiple pathogens. Studies providing information on the epidemiology of bacterial or viral infections in pregnant women were identified but not analyzed, as they were addressed in a separate review. Relevant English language papers were analyzed in this work, along with Chinese electronic databases, with the intention of translating and analyzing non-English papers, too. The inclusion criteria were:

Subjects: Pregnant women at any stage of pregnancy or labour, including the puerperium (up to 42 days after labour);

Study location: Low- and middle-income countries (as defined by the World Bank in 2010);

Study design and sampling methods: No restrictions applied;

Data collection: Only studies that provided evidence of parasitic infection using microbiological or serological test results were included;

Results: Papers were selected if they provided information on the burden of a particular pathogen (the prevalence of a particular infection in pregnant women in the community over time/incidence) and/or the aetiology of parasitical maternal infections (prevalence of a specific pathogen/infection).

Quality criteria

Papers were required to describe their samples and methods in detail, and provide microbiological or serological evidence of the aetiology of infection.

Data extraction

Information on pathogen studied, sample population (pregnant women studied during pregnancy or at labour) and size, study setting, duration and type, microbiological/serological test used and results were extracted from abstracts and full papers for analysis.

Data analysis

Epidemiology and aetiology of maternal parasitic infections were summarized according to the pathogen studied. Only pathogens with 5 or more studies reporting on its epidemiology and/or aetiology were analyzed. Median prevalence of each infection was calculated and trends in the prevalence of maternal infections were noted.

Selection of studies

The final search yielded 8580 relevant titles. **Figure 1** outlines the results of the search process and application of inclusion and exclusion criteria, resulting in the final panel of studies from which data was extracted.

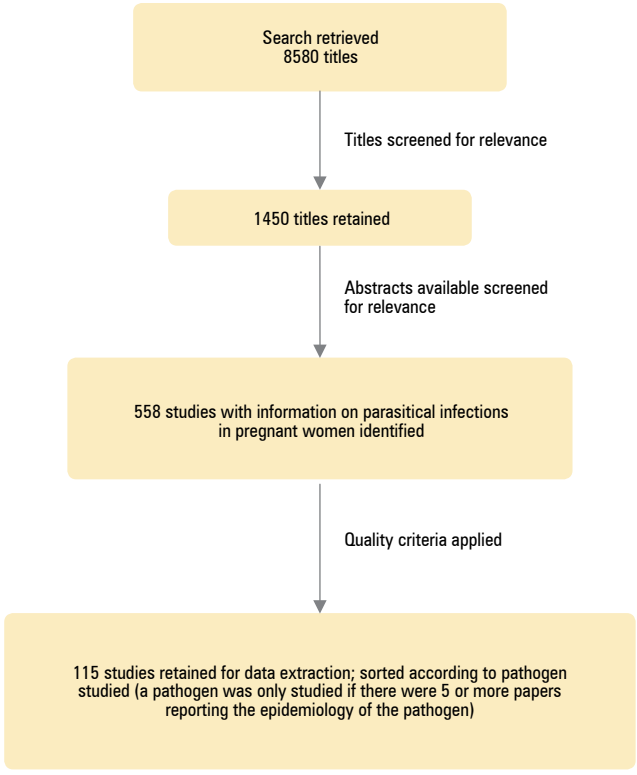


Figure 1 Summary of the literature search conducted.

Studies retained for data extraction (n=115) characterized the prevalence of 6 parasitic pathogens (malaria, helminths, *Toxoplasma gondii,* Chagas disease, trichinellosis and *Trichomonas vaginalis*) among pregnant women in developing countries, with 3 further reports providing secondary cross-sectional insights or reviews of the literature in this field, which were considered useful (4–118).

RESULTS

Prevalence of parasitical infections

Malaria. We identified 43 studies characterizing the prevalence of maternal malaria in 19 developing countries (**Supplementary Table 1**). The features and results of these studies are summarised in **Table 2** and **Figures 2** to **4**.

The majority of studies had small sample sizes (**Table 2**), between 0–500 subjects and most of them were conducted in antenatal clinics or hospitals (82.7%), suggesting either awareness towards the need for antenatal screening for maternal malaria infection, or merely that it is much easier to recruit study subjects in health care facilities. The remaining studies (8.9%) were community-based and the study setting was not specified in 8.4%.

Blood smears with Giemsa stains were by far the most regularly used diagnostic test, accounting for 47% of all tests

Table 2 Distribution according to the size of population studied in 43 studies reporting maternal malaria prevalence

Size of population	Number (%)
0–500	28 (65%)
501–1000	6 (14%)
1001–1500	4 (9%)
1501–2000	0 (0%)
2001–2500	0 (0%)
2501–3000	1 (2%)
3001–3500	0 (0%)
3501–4000	1 (2%)
4001–4500	1 (2%)
4501–5000	0 (0%)
>5000	2 (5%)

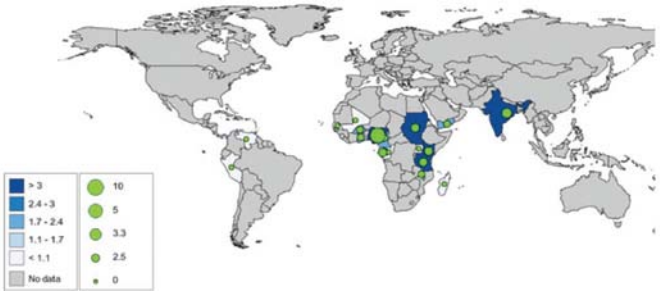


Figure 2 Geographical distribution of studies (n=43) reporting the prevalence of maternal malaria. "No data" in the legend refers to low- and middle-income countries only, as data from high-income countries were not the subject of this study.

used to detect Malaria (**Figure 3**). Very high prevalence, of *Plasmodium vivax* (78.69%) was found in Brazil (28). Nine studies in seven different countries reported prevalence of over 50%: Gabon (57% and 54%) India (55%), Cameroon (50%), Yemen (55%), Nigeria (57% and 64%) and Ghana (54%) (26,29,39,46,47,49,51). The mean prevalence of malaria, regardless of the blood site taken from, was between 20–30%, suggesting a degree of consistency between tests from different blood sites (**Figure 4**).

Helminths. Fourteen studies characterizing the prevalence of maternal infections with helminths in 11 developing countries were identified (**Supplementary Table 2**). The features and results of these studies are summarised in **Table 3** and **Figures 5** to **7**.

The majority of studies had small sample sizes (**Table 3**), between 0–500 subjects and most of them were conducted in antenatal clinics or hospitals (75%), suggesting either awareness towards the need for antenatal screening for maternal malaria infection, or merely that it is much easier to recruit study subjects in health care facilities. The remaining studies (18%) were community-based and the study setting was not specified in 9%.

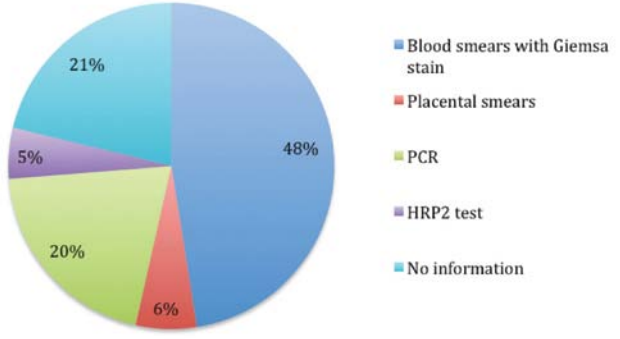


Figure 3 Techniques used to diagnose maternal malaria in the 43 studies identified. PCR – polymerase chain reaction, HRP2 test – histidine-rich protein 2.

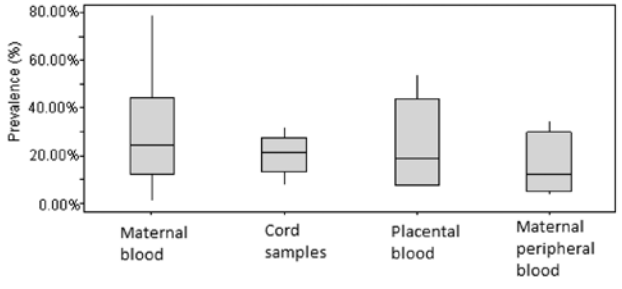


Figure 4 Box plot of malaria prevalence in different blood samples, reported by 43 relevant studies. The following number summaries are depicted in the box plot: sample minimum, lower quartile, median, upper quartile, and sample maximum.

Table 3 Distribution according to size of population studied in 14 studies reporting maternal infection with helminth prevalence

Size of population	Number (%)
0–500	9 (69%)
501–1000	0 (0%)
1001–1500	1 (8%)
1501–2000	0 (0%)
2001–2500	1 (8%)
2501–3000	2 (15%)
3001–3500	0 (0%)
3501–4000	0 (0%)
4001–4500	0 (0%)
4501–5000	0 (0%)
>5000	0 (0%)

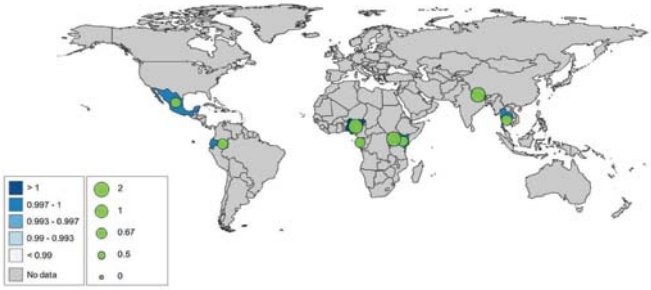


Figure 5 Geographical distribution of studies (n=14) reporting the prevalence of maternal infection with helminths. "No data" in the legend refers to low- and middle-income countries only, as data from high-income countries were not the subject of this study.

Between the studies there was a generalised trend to use the Kato-Katz technique for examining stool samples (**Figure 6**), which is the gold standard for an epidemiological survey of helminth eggs (119). The prevalence of the different helminths varied across the studies. The most prevalent was hookworm, with a mean prevalence of 45%. The highest prevalence of hookworm infections was found in Nepal at 78.8% and high values were found in Uganda (44.5% and 45% in 2 studies), Tanzania (56.3%) and Kenya (39.5%) (12,16,18,19,24). For *Ascaris lumbricoides* relatively high prevalences were found in Nepal, (56.2%), Kenya (52.3%) and Gabon (45.5%) (11,18,19). *Trichuris trichiura* was least prevalent with a highest prevalence of 31% in Gabon and a mean value of 13% (11). High levels of *Schistosoma mansoni* were found in Zimbabwe (50%) and Tanzania (63.5%), but the prevalence in other countries was typically around 30% (10,24) (**Figure 7**).

Toxoplasma gondii. Forty-nine studies characterizing the prevalence of maternal infections with *T. gondii* in 26 developing countries were identified (**Supplementary Table 3**). The features and results of these studies are summarised in **Table 4** and **Figures 8** to **10**.

The majority of studies had small sample sizes (**Table 4**), between 0–500 subjects. Twenty five percent of the studies

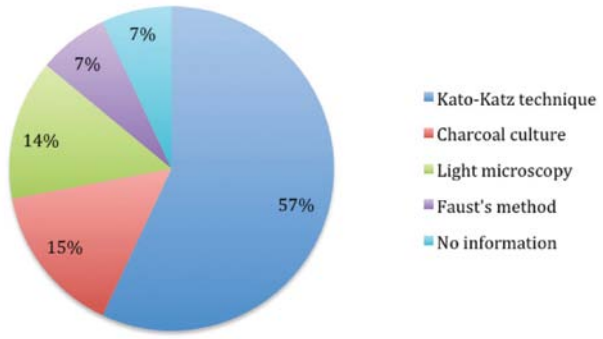


Figure 6 Techniques used to diagnose maternal infection with helminths in 14 studies identified.

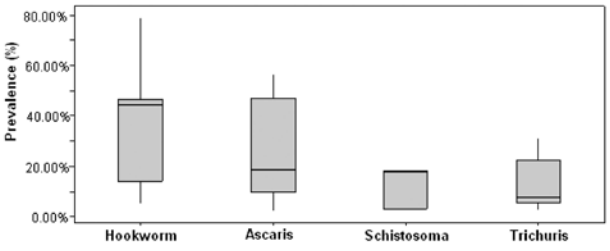


Figure 7 Box plot of the prevalence of maternal infections with helminths reported by the 14 relevant studies. The following number summaries are depicted in the box plot: sample minimum, lower quartile, median, upper quartile, and sample maximum.

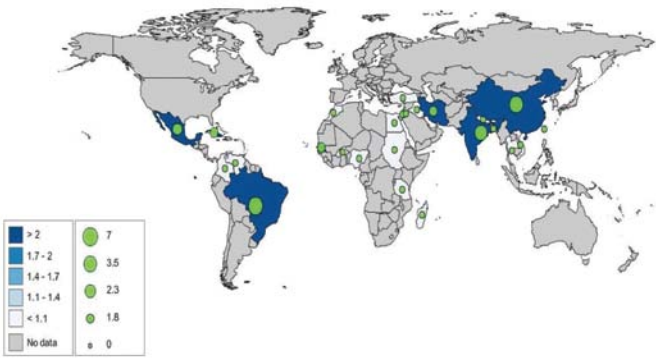


Figure 8 Geographical distribution of studies (n=49) reporting the prevalence of maternal infection with *Toxoplasma gondii*. "No data" in the legend refers to low- and middle-income countries only, as data from high-income countries were not the subject of this study.

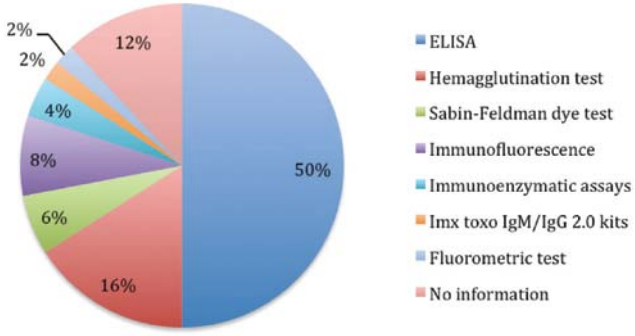


Figure 9 Techniques used to diagnose maternal infection with *Toxoplasma gondii* in 49 studies identified.

Table 4 Distribution according to size of population studied in 48 studies reporting maternal infection with *Toxoplasma gondii* prevalence

Size of population	Number (%)
0–500	29 (60%)
501–1000	6 (13%)
1001–1500	4 (8%)
1501–2000	1 (2%)
2001–2500	2 (4%)
2501–3000	0 (0%)
3001–3500	0 (0%)
3501–4000	0 (0%)
4001–4500	1 (2%)
4501–5000	1 (2%)
>5000	4 (8%)

were conducted in antenatal clinics, hospitals, health care facilities or prenatal clinics. The remaining studies (2%) were community-based and the study setting was not specified in 75% of the studies.

The most commonly used test was ELISA, which is the gold standard for *T. gondii* analysis (**Figure 9**). The prevalence of both IgG and IgM was measured in 22 out of the 49 studies, useful for analysing current (IgM) and past (IgG) infections in pregnant mothers. The prevalence of active infection was low with a mean of 4% but there were high levels in India (27.7%), Mexico (20.7%) and Sudan (14.3%). The mean IgG (past infection) prevalence was 39%, highest prevalence in Brazil (75.1%) (**Figure 10**).

Chagas disease. Seven characterizing the prevalence of maternal infections with Chagas disease in 7 developing countries were identified (**Supplementary Table 4**). The features and results of these studies are summarised in **Table 5** and **Figures 11** to **13**.

The majority of studies had small sample sizes (**Table 5**), between 0–500 subjects. Fourteen percent of the studies were conducted in hospitals, 29% in endemic and 29% in non-endemic areas. The remaining studies (14%) were conducted in parturient and the study setting was not specified in 14% of the studies.

The most commonly used tests were indirect immunoflouresence and indirect haemogluttination tests (**Figure 12**). Chagas disease had a low mean prevalence of around 7.2% in pregnant women but a study in Bolivia (9) reported a prevalence of 26.3% (**Figure 13**).

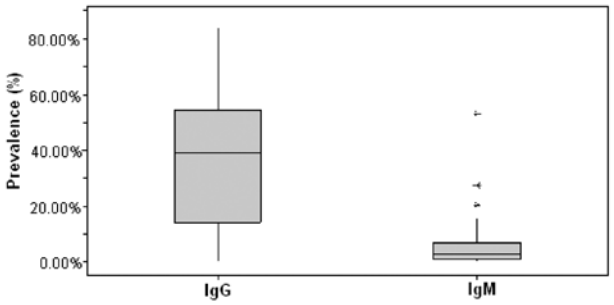


Figure 10 Box plot of maternal infections with Toxoplasma *gondii* prevalence reported by 48 relevant studies. The following number summaries are depicted in the box plot: sample minimum, lower quartile, median, upper quartile, and sample maximum. Asterisks indicate outliers.

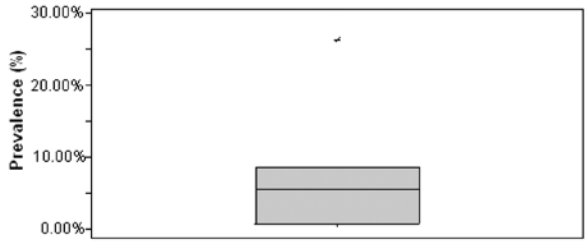


Figure 13 Box plot of maternal infections with Chagas disase prevalence reported by the 749 relevant studies. The following number summaries are depicted in the box plot: sample minimum, lower quartile, median, upper quartile, sample maximum. Asterisk indicates an outlier.

Figure 11 Geographical distribution of studies (n=7) reporting the prevalence of maternal infection with Chagas disease. "No data" in the legend refers to low- and middle-income countries only, as data from high-income countries were not the subject of this study.

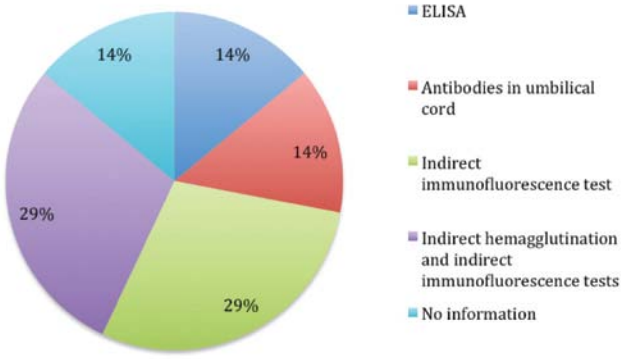


Figure 12 Techniques used to diagnose maternal infection with *Toxoplasma gondii* in the 49 studies identified.

Trichinellosis. There was only one study looking at trichinellosis (**Supplementary Table 5**). Because of the scarcity of studies it is hard to make any inference to trends, so more research needs to be done in this area.

Trichomonas vaginalis. We found only four studies focused on trichomoniasis (**Supplementary Table 6**). Because of the scarcity of studies it is hard to make any inference to trends and more research is needed.

Table 5 Distribution according to size of population studied in 7 studies reporting maternal infection with Chagas disease prevalence

Size of population	Number (%)
0–500	1 (14%)
501–1000	2 (29%)
1001–1500	0 (0%)
1501–2000	0 (0%)
2001–2500	3 (43%)
2501–3000	0 (0%)
3001–3500	1 (14%)
3501–4000	0 (0%)
4001–4500	0 (0%)
4501–5000	0 (0%)
>5000	0 (0%)

DISCUSSION

Prevalence of parasitic infections

Our search of published literature relevant to the aetiology and epidemiology of maternal parasitic infections in the developing world provided detailed epidemiological information on 6 maternal infections. These 6 parasitical maternal infections were most extensively studied, suggesting that these infections have a high burden on pregnancy outcomes in the developing world. These infections also have potential adverse effects on neonates.

Malaria in its own right is a major contributing factor towards maternal deaths worldwide. It causes severe anaemia and can affect newborn's birth-weight and long-term survival (119). For this reason, it is recommended that research conducted in South and Central America, especially Brazil where the prevalence of *P. vivax* was so high (78.69%) to be expanded (28). Further research should also be concentrated on regions classified as high risk but with a current lack of data like Democratic Republic of Congo, Angola and Zambia, from where no evidence of research was found. Finally, prevention strategies should be encouraged in the maternal populations from the countries with evidence of very high malaria prevalence, namely Gabon, India, Cameroon, Yemen, Nigeria and Ghana (26,29, 39,46,47,49,51).

Hookworm infections were found to be well studied, which is very promising as these parasites cause anaemia during pregnancy and have been noted to increase the maternal and child mortality rates (120). However more studies looking at *Schistosoma* would definitely be recommended as there were only 4 studies in pregnant women, despite WHO's statement that *Schistosoma* is "second only to malaria in public health importance" and pregnant women are one of the important at risk groups (121). Specific countries of note for further investigation and preventative measures would be Nepal for hookworms (78.8%) and *A. lumbricoides* (56.2%) (19); Tanzania for hookworms (56.3%) and *Schistosoma mansoni* (63.5%) (24); Kenya for hookworms (39.5%) and *A. lumbricoides* (52.3%); the Gabon for *A. lumbricoides* (45.5%) and *Trichuris trichuria* (31%); and finally for *S. mansoni* (50%) (10,11,18).

Chagas disease is important because of its potential to cause mortality in all age-groups. It can be transmitted vertically so that the knowledge of maternal prevalence is important (122). Although this review has shown studies in South America, the disease is no longer confined to just South America, as with Latino American emigration there has been a movement of the disease across the world. Therefore global research in areas of high Latino American immigration would be recommended to assess the extent this emigration has had (123). More funding in Bolivia would be recommended to assess the nature of the 26.3% prevalence of maternal infection and its effects on maternal and neonatal health (9).

There is a need for more studies on *Leishmania*. Although not much evidence can be taken from the single study from Brazil (124), pregnant woman tended to have more severe *Leishmania* than the non-pregnant infected subjects and there was a possible link with increased problems with pregnancy.

Strengths and limitations

To our knowledge, this is the first review that summarises the epidemiology of maternal parasitic infections in the developing world. The search strategy devised was sensitive and specific, which allowed for a comprehensive review of available literature on this topic. The information generated in this review can be used to guide public health policy and the allocation of resources within local governments and by the international community towards improving maternal health. Although the search did not exclude non-English papers, we did not search some of the databases where we would have expected a higher concentration of foreign language papers (e.g. LILACS). Although the databases used were very extensive, especially in the case of EMBASE and Medline there is a high chance that important papers could have been recovered from smaller, more specialist databases.

This study could be further improved by analysing non-English studies conducted in francophone parts of Africa (in French), South America (in Spanish) and in China (in Chinese), which could be accessed from appropriate databases. Reviewing non-English articles may assist in defining the epidemiology of pathogens for which we managed to identify few (<5) studies, as well as providing more robust data on the pathogens presented in this review. In addition, searching grey (unpublished) literature or contacting health officials and researchers in the field may also yield more country specific data on the subject, thus enabling more targeted and context-specific public health measures.

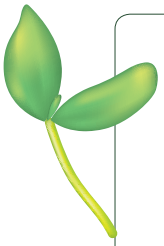
Recommendations and future work

This systematic review highlights the quantity of maternal parasitic infection research and, to a lesser extent, quality of research that has been achieved over the last 30 years. This paper would therefore be useful to decision makers, especially in light of the US$ 40 billion (€ 30 billion) pledged at the last UN's MDG summit, to help them assess where best to implement resources for research. It could also be a useful tool to measure how good the data is for each individual parasite and in assessing what areas of the world have been neglected in terms of research. With a full picture where different maternal infections occur, it could be used as a tool to target research and could ultimately lead to big leap forward maternal infections knowledge, therefore helping in the fight towards cutting down maternal infections.

Conclusion

No mother should die during childbirth and every step should be taken to stop this happening. This review is a first step, in a long chain of events, trying to prevent maternal mortality. If research and knowledge is channelled into the right areas and decision makers have accurate knowledge regarding maternal infections then resources can be allocated to those areas that need it most.

Researchers have a responsibility to reflect on which part of the world current knowledge is stemming from and should look retrospectively to see how much research has been done in the past. By doing this, the public health community can positively expand research into areas of the world and into diseases where that information is lacking. And with this information, informed and important decision can be made about the factors that affect maternal mortality most and maybe, just maybe, Millennium Development Goal 5 can be achieved.



Acknowledgements: We thank Shiela Fiskin, librarian, for her advice on databases and refining of search terms and Edinburgh medical student Pascal Geldsetzer.

Funding: Bill and Melinda Gates Foundation.

Ethical approval: Not required.

Authorship declaration: All authors designed and conducted the study and contributed to the writing of the paper.

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 support from Bill and Melinda Gates Foundation for the submitted work. The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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Biomarkers for diagnosis of neonatal infections: A systematic analysis of their potential as a point-of-care diagnostics

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Background Neonatal infections annually claim lives of 1.4 million neonates worldwide. Until now, there is no ideal diagnostic test for detecting sepsis and thus management of possible sepsis cases often depends on clinical algorithm leading to empirical treatment. This often results in unnecessary antibiotic use, which may lead to emergence of antibiotic resistance. Biomarkers have shown great promise in diagnosis of sepsis and guiding appropriate treatment of neonates. In this study, we conducted a literature review of existing biomarkers to analyze their status for use as a point-of-care diagnostic in developing countries.

Methods PubMed and EMBASE database were searched with keywords, 'infections', 'neonates', and 'biomarkers' to retrieve potentially relevant papers from the period 1980 to 2010. Leading hospitals and manufacturers were communicated to inquire about the cost, laboratory requirements and current standing of biomarkers in clinical use.

Results The search returned 6407 papers on biomarkers; 65 were selected after applying inclusion and exclusion criteria. Among the studies, C-reactive protein (CRP), procalcitonin (PCT) and interleukin 6 (IL-6) were the most widely studied biomarkers and were considered to be most promising for diagnosing neonatal infections. About 90% of the studies were from developed countries; more than 50% were from Europe.

Conclusions Extensive work is being performed to find the diagnostic and prognostic value of biomarkers. However, the methodologies and study design are highly variable. Despite numerous research papers on biomarkers, their use in clinical setting is limited to CRP. The methods for detection of biomarkers are far too advanced to be used at the community level where most of the babies are dying. It is important that a harmonized multi-site study is initiated to find a battery of biomarkers for diagnosis of neonatal infections.

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Most developing countries have witnessed substantial declines in mortality among children <5 years of age (1,2). In contrast, neonatal mortality has remained relatively constant, with an estimated 3.6 million annual neonatal deaths globally (2–5). Neonatal mortality now accounts for about 40–50% of under-five child deaths (4–6). More than 90% of these deaths occur in the poorest countries of Asia and Africa (7). Suspected infections,

including sepsis, pneumonia and meningitis (hereafter referred to as "infections") account for an estimated 1.4 million neonatal deaths worldwide every year (5,6).

Low and middle income countries are trying different modalities to achieve MDG4 by 2015. The common intervention is community-based diagnosis of possible sepsis cases, using clinical algorithms and treatments with empiric antibiotics. Highly sensitive algorithms based therapies have performed well in reducing child mortality, irrespective of the antibiotic therapy used (6,8). However, blood culture, as the gold standard for diagnosis, from these algorithm-positive cases yielded bacterial isolates only in 5–10% of cases. This jeopardized the credibility of the "gold" standard. In recent years, with the advancement of these techniques like real time polymerise chain reaction (RT-PCR) for specific genome and broad range targets, the use of molecular approaches has become common for aetiological diagnosis (9). Although a recent meta-analysis showed that the molecular tests cannot increase the detection frequency of aetiology more than what blood culture already captures (9). Hence it is becoming increasingly important to find a tool to differentiate sick newborns with or without infection, especially to minimize the indiscriminate use of antibiotics. In the last few years, biomarkers, triggered by the host immune system in response to infections, have been targeted as potential indicator for diagnostic and prognostic purposes.

This study was taken up to conduct a structured literature overview on the existing biomarkers for diagnosis of neonatal infections/sepsis and to elucidate their relative potential to be used in resource-poor settings. In addition, the study also investigated the instrumental requirements for detection of biomarkers and the extent of their use in clinical practice.

METHODS

Selection of biomarkers for analysis

After a preliminary examination of the available literature, we consolidated the list of biomarkers for further review. These markers were selected based on the number of papers published on the topic and their potential to be used for diagnosis and prognosis of neonatal infection. Biomarkers included in this analysis are as follows:

Acute phase proteins: C– reactive protein (CRP), procalcitonin (PCT);

Cytokines: interleukin 6 (IL-6), interleukin 8 (IL-8), interferon – gamma (IFN-γ), tumor necrosis factor – alpha (TNF-α);

Cell surface antigens: CD 64, soluble intercellular adhesion molecule (sICAM).

Search strategies

In order to carry out a landscape analysis to identify studies on the diagnostic performance of the aforementioned biomarkers, we searched PubMed and EMBASE bibliography databases. Search strategies for both databases were carefully built to maximize the sensitivity of our search. A combination of text words and subject heading terms specific to each database (MeSH terms for PubMed and EMTREE terms for EMBASE) were used to develop the search strategy (**Table 1**).

The search strategy also adapted individual biomarker specific final queries and ran the search to ensure retrieval of

Table 1 Search strategy, restricted to age (newborn), subject (humans) and time period (January 1980 to April 2010)

EMBASE:	('newborn'/exp OR newborn OR 'newborn'/syn OR 'newborns':ab,ti OR 'neonates':ab,ti OR 'infants':ab,ti) AND ('infection'/exp OR infection OR 'infection'/syn OR 'infections' OR 'sepsis'/exp OR sepsis OR 'sepsis'/syn OR 'bacterial infection'/exp OR 'bacterial infection' OR 'infections':ab,ti OR 'bacterial infection'/syn OR 'bacteremia'/exp OR bacteremia OR 'bacteremia'/syn OR 'septicemia'/exp OR septicemia OR 'septicemia'/syn OR 'systemic inflammatory response syndrome'/syn OR 'systemic inflammatory response syndrome'/exp OR 'systemic inflammatory response syndrome' OR 'meningitis'/exp OR 'meningitis' OR 'meningitis'/syn) AND ('c reactive protein'/exp OR 'c reactive protein' OR 'c reactive protein'/syn OR 'procalcitonin'/exp OR procalcitonin OR 'pct':ab,ti OR 'tumor necrosis factor alpha'/exp OR 'tumor necrosis factor alpha' OR 'tumor necrosis factor alpha'/syn OR 'tnf alpha' OR 'tnf-alpha':ab,ti OR 'gamma interferon'/exp OR 'gamma interferon' OR 'gamma interferon/syn' OR 'ifn-gamma':ab,ti OR 'ifn gamma':ab,ti OR 'intercellular adhesion molecule 1'/exp OR 'intercellular adhesion molecule 1' OR 'intercellular adhesion molecule 1'/syn OR 'icam 1':ab,ti OR 'cd64 antigen'/exp OR 'cd64 antigen' OR 'cd64 antigen'/syn OR 'cd64':ab,ti OR 'interleukin 6'/exp OR 'interleukin 6' OR 'interleukin 6'/syn OR 'il 6':ab,ti OR 'il-6':ab,ti OR 'interleukin 8'/exp OR 'interleukin 8' OR 'interleukin 8'/syn OR 'il 8':ab,ti OR 'il-8':ab,ti) AND ('diagnosis'/exp OR diagnosis OR 'diagnosis'/syn OR 'biological marker'/exp OR 'biological marker' OR 'biological marker'/syn OR markers:ab,ti OR biomarkers:ab,ti OR test:ab,ti OR tests:ab,ti OR indicators:ab,ti)
PubMed/ Medline:	(neonat* [tw] OR newborn [mh] OR newborn [tw] OR newborns [tw] OR neonate [tw] OR neonates [tw] OR baby [tw] OR babies [tw] OR infant [tw] OR Infants [tw]) AND ("sepsis" [mh] OR sepsis [tw] OR "bacterial Infections" [mh] OR (septic [tw] AND shock [tw]) OR "systemic inflammatory response syndrome" [mh] OR "systemic inflammatory response syndrome" [tw] OR infection [tw] OR infections [tw] OR bacteremia [tw] OR bacteraemia [tw] OR bacteremias [tw] OR bacteraemias [tw] OR septicemia [tw] OR septicemias [tw] OR septicaemia [tw] OR septicaemias [tw] OR bacteremic [tw] OR bacteraemic [tw] OR bacterial [tw] OR viremia [tw] OR viremias [tw] OR viraemia [tw] OR viraemias [tw] OR Viremic [tw] OR viraemic [tw] OR fungemic [tw] OR fungemia [tw] OR fungemias [tw]) AND (("Diagnosis" [mh] AND (markers [tw] OR marker [tw])) OR markers [tw] OR marker [tw] OR "biological markers" [mh] OR biomarker [tw] OR biomarkers [tw] OR ("sensitivity and specifity" [mh] AND (sensitivity [tw] OR specificity[tw])))

maximum papers. A total of 4868 citations from PubMed and 1539 citations from EMBASE were retrieved. These references were imported into separate libraries using the EndNote software (Thomson Reuters, Philadelphia, PA, USA). The libraries were later merged, and the duplicates were removed. Two reviewers independently screened the titles and abstracts of the retrieved citations to find the articles that were deemed relevant.

Inclusion criteria

For inclusion, the abstract and titles were screened based on the following predetermined criteria: i) the subject population is newborns, ii) the subjects are with culture proved sepsis or suspected infection based on clinical algorithm and iii) the article evaluated any of the proposed biomarkers for diagnosis and/or prognosis of neonatal infections.

The exhaustive search based on the titles and abstracts returned a broad spectrum of infection related studies from which only the cases of sepsis, urinary tract infection, meningitis, pneumonia, respiratory tract infections and umbilical cord infections were considered.

Finally, full text articles with following criteria were included for analysis: i) the age of the newborns ranged from 0 days to 59 days and ii) diagnostic performance of target biomarkers are explored in clinical and/or in culture-confirmed cases of sepsis.

Exclusion criteria

It was challenging to select the relevant articles for this analysis from the large number of papers retrieved (n=6407) based on the above mentioned selection criteria. To make a comprehensive list of appropriate papers, we excluded the articles that dealt with malaria, HIV infection, hepatitis, toxoplasmosis, gestational diabetes, bronchopulmonary dysplasia, antenal and maternofetal studies, in-vitro studies, transplant immunology studies, polymorphisms, necrotizing enterocolitis, foreign languages other than English, letters, comments and editorials and other non-research publication types.

Data extraction

Available full papers were downloaded from PubMed, EMBASE and HINARI sources. Requests for reprints were sent to the authors of the papers which were not available from these sources. Data were extracted and compiled in Excel spreadsheet with the following column headings: Name of Biomarker, Study Title, First Author, Year, Setting, Country, Clinical Characteristics, Sample Size, Age, Specimen source, Method, Cut off, Cost, Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV).

For a point of reference, we contacted the leading hospitals of several developed and developing countries to learn what tests/biomarkers are currently being used at their clinical settings. We also contacted major diagnostics manufacturers to inquire about the direct costs and laboratory requirements for assaying each of the biomarkers.

RESULTS

Out of 705 potentially relevant papers, 65 were selected for final review after exclusion of 640 papers for the lack of sufficient information, ambiguity in study design and patient characteristics, failure to obtain full-text article or absence of other inclusion criteria (**Figure 1**).

Prevalence of research on biomarkers

Review of relevant papers, published during January1980 to April 2010, revealed that CRP was the most extensively studied biomarker (n=396), followed by IL-6 (n=157), PCT (n=107), TNF-alpha (n=80), IL-8 (n=72), sICAM (n=20), CD64 (n=14), IFN-γ (n=9) **(Figure 2).** However, even the less frequent markers showed promise in respect of their ability to differentiate the sepsis from non-sepsis cases.

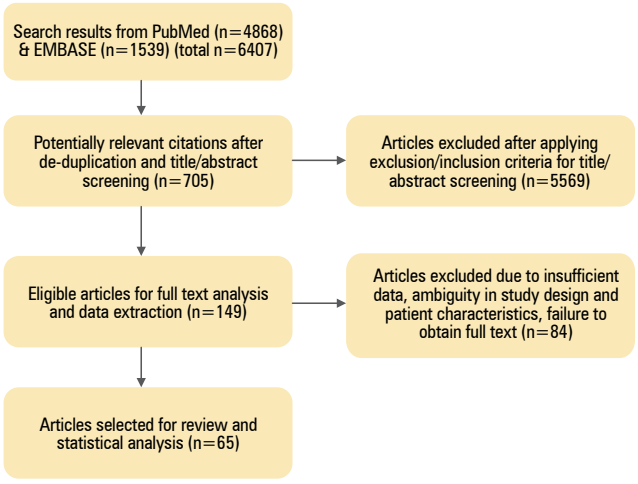


Figure 1 Search strategy and identified articles.

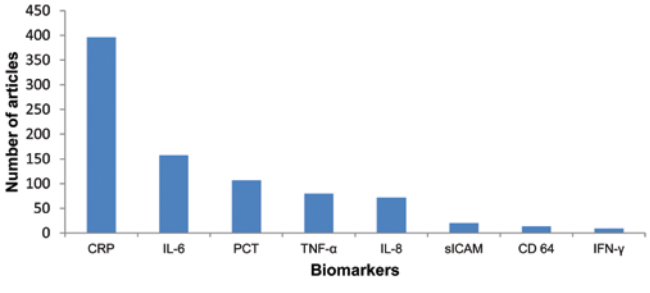


Figure 2 Distribution of studies according to biomarkers studies. CRP – C-reactive protein, IL – interleukin, TNF – tumor necrosis factor, sICAM (soluble intercellular adhesion molecule, IFN – interferon.

Heterogeneity of the studies

Biomarker research studies widely differed by study groups in respect to their inclusion criteria for patients, case definition, test methodologies and cut off values for markers (**Table 2**). The range of cut off value was as wide as 0.2 to 95 mg/mL for CRP, 0.34 to 100 ng/mL for PCT, 3.6 to 500 pg/mL for IL-6; and 1 to 1000 pg/mL for IL-8. Accordingly, sensitivity and specificity of the tests also varied widely among the studies. For convenience of interpretation of sensitivity and specificity, we divided the studies in smaller subgroups based on their cut off values used by the study groups (**Table 2**).

Characteristics of biomarkers

The mean cut-off point of CRP was 17 mg/L, with 66% sensitivity and 86% specificity. PCT appeared to be a more relevant marker than CRP for diagnosing bacterial sepsis at earlier stages, with the mean sensitivity of 77.93%, specificity of 81.84%, and a cut-off of 8.92 ng/mL. For IL-6, the mean sensitivity at "zero hour" was 77.87%, specificity was 78.61%, and the mean cut- off value was 76.49 pg/mL (**Table 2**). The mean value of cut-off for IL-8 was 220.53 pg/mL, sensitivity 72.48% and specificity 80.57% (**Table 2**).

CRP and PCT have been extensively studied and compared for their efficacy to diagnose sepsis cases in young infants. Overall, the studies reported that the optimum sensitivity and specificity for CRP was obtained during the window of 24–48 hours after the onset of symptoms. On the other hand, PCT was sensitive enough to detect the cases much earlier than CRP. However, some studies also suggested that serial measurements of CRP over a period of 2–3 days after onset clinical symptom, using varying cut-off values, improved the diagnostic performance of CRP (10,11).

CD64 demonstrated the mean sensitivity of 92% and a specificity of 82.79% during the first 24 hours of infection. sICAM yielded the mean sensitivity of 79% and specificity of 75.5%. Finally, the mean sensitivity of TNF-α was 78.72%, and the specificity was 81.4% (**Table 2**). Unfortunately, we could not find any analyzable data for IFN-γ from any of the relevant studies.

Minimum laboratory requirements and cost analysis

According to retrieved studies, the major techniques for detecting biomarkers were immunoassays, and cell sorting for CD64. The immunoassays were usually accompanied by a variety of readers to quantify the level of specific markers. Most of the studies used enzyme-linked immunosorbent assay (ELISA) readers for quantification along with other tests like immunoturbidimetric and nephelometric assays. These methods, except ELISA, were rarely available at the resource-poor settings.

The detection method for CRP as the extensively studied and widely used marker was also immunoassay, usually using an ELISA reader. In resource-poor settings, qualitative or semi-quantitative latex agglutination test is also used for the detection of CRP. Other immunoassays are only available at the tertiary level and/or private commercial facilities in low income countries. Some studies used immunoluminometry and chemiluminescence for the detection of PCT.

Table 2 Sensitivity, specificity and cut-off values of biomarkers in reviewed studies*

Biomarker	Cut-off range	Cut-off sub-ranges	Percentage of papers	Sensitivity ranges (%)	Specificity ranges (%)	Cut-off	Sensitivity	Specificity
CRP	0.2–95 mg/L	0.2–10	70	41–96	72–100	mean=17. 1median=10	mean=66.53 median=69 (IQR=26.3)	mean=86.14 median=90 (IQR=13.9)
		11–30	15	33–56	74–96			
		31–95	15	23–87	48–98			
PCT	0.34–100 ng/mL	0.34–1.0	48	58–100	50–100	mean=8.92 median=1.17	mean=77.93 median=8 (IQR=14.8)	mean=81.84 median=82.5 (IQR=16.6)
		2–10	39	59–95	50–100			
		11–100	13	21–95	87–100			
IL-6	3.6–500 pg/mL	2–10	15	88–96	66–89	mean=76.49 median=30	mean=77.87 median=80 (IQR=29.9)	mean=78.61 median=78 (IQR=18.9)
		11–30	34	61–90	56–90			
		31–100	31	57–100	43–100			
		101–500	20	74–97	70–100			
IL-8	1–1000 pg/mL	0.6–100	74	34–92	52–96	mean=220.53 median=70	mean=72.48 median=80 (IQR=15.5)	mean=80.57 median=82 (IQR=21.7)
		101–1000	26	36–92	65–96			
CD64	different units used	–	–	79–100	81–96.8	not analyzable	mean=82.42 median=92 (IQR=17)	mean=82.79 median=88 (IQR=15)
sICAM	250–300 µg/L	–	–	78–80	61–90	mean=275 median=275	mean=79 median=79 (IQR=1)	mean=75.5 median=75.5 (IQR=14.5)
TNF-α	1.7–70 pg/mL	–	–	54–100	43–96.6	mean=18.94 median=7.5	mean=78.72 median=80.4 (IQR=22.7)	mean=81.4 median=93 (IQR=14.9)

CRP – C-reactive protein, IL – interleukin, TNF – tumor necrosis factor, sICAM (soluble intercellular adhesion molecule, IFN – interferon, IQR – interquartile range.

*Reported in refs 13–77.

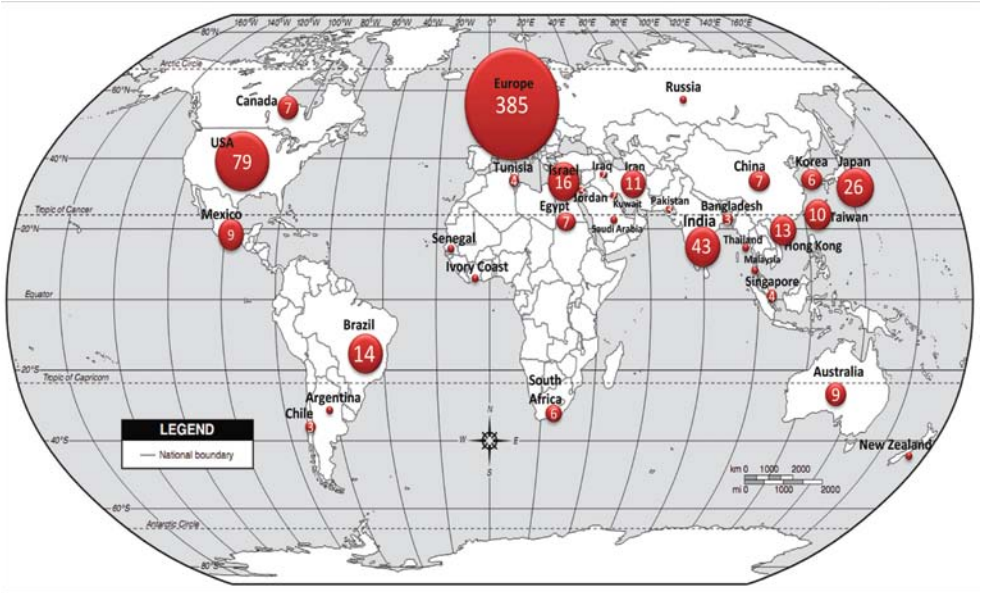


Figure 3 Geographical distribution of published research on biomarkers in the last three decades (January 1980 to April 2010).

Immunochromatographic tests (ICT) was also reported for PCT in a few studies, but these were still at the developmental stage and only at research level (12). Flow cytometry was invariably used by all the studies for detection of cell surface antigen CD64 and the literature revealed very little information about the cost associated with these techniques (13–77).

Global distribution of biomarker research

We tried to establish the geographical distribution of biomarker research based on retrieved studies. Research on biomarkers was mostly confined to the developed countries with a large share of the total numbers of articles (385/705, 55%) from Europe, followed by North America (95/705, 13%). In contrast, only 9.5% (68/705) papers were from South Asia and Africa (**Figure 3**); the regions where more than a third of neonatal deaths occur.

DISCUSSION

Biomarkers may have great potentials for diagnosis of neonatal sepsis and have been studied for more than two decades. The frontiers of research in biomarkers as diagnostic tools for detecting neonatal sepsis have progressed considerably over the years and persist in advancing novel technologies. This review suggests that many newer biomarkers have come into play, and thorough investigations on them are in progress.

Among the numerous biomarkers in the field of neonatal sepsis diagnosis, this review identified 8 predominant markers, as determined by number of publications: CRP, PCT, IL-6, IL-8, IFN-γ, TNF-α, CD64 and sICAM. Of these, CRP was the most widely used diagnostic and prognostic marker. Despite its limitation due to late appearance and persistence for relatively longer period (76), it was used as the standard marker to measure the potential and efficacy of newer biomarkers. Among other markers, PCT has come up as more promising, with the comparative advantage of early detection in sepsis and quick reduction in its levels in response to appropriate therapy (72). PCT also has the additional advantage of being specifically responsive to bacterial infections and not viral (73). On the other hand, IFN-γ seems to be particularly responsive to viral infection at very early stage of infection (74).

Based on the available data about the detection time, the markers could be classified into three groups; early phase (IL-6, IL-8, CD64, sICAM, TNF-α and IFN-γ), mid phase (PCT) and late phase (CRP). The unique dynamics of appearance and disappearance of specific markers would be useful for possible multiplexing to capture the neonatal infection cases irrespective of their disease status.

Other biomarkers have also showed promise, and most of them revealed potential for detection of sepsis at very early stage of the disease. IL-6 demonstrated a high potential with the ability to detect the cases at very early stage of infection and monitor the appropriateness of therapy, based on its characteristic early appearance and short half life (75). Newer markers like sICAM and CD64 also have the potential to detect sepsis cases at very early stage of disease, with high sensitivity but compromised specificity (57–62).

With all possible and definite potentials of biomarkers, none of them is currently in use for patient care, except

CRP. The review identified several reasons for this slow transition of biomarkers from the research laboratories to their real-life use in clinical care. The main cause of this hindrance is the heterogeneity between the research protocols used by different groups. The study designs are heterogenic with respect to cut off values used to define positivity, which sometimes varied by about 100 folds (**Table 2**). In some studies different threshold levels were used for same biomarker, based on the duration of illness at the time of collection of blood (10,11). This is an impractical approach to be implemented at any clinical setting.

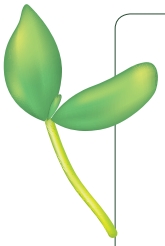
Defining "zero hour" is an important parameter to characterize the biomarkers as early or late infection detectors. However, this definition varied from study to study as it was mostly decided based on the blood collection time, and only few studies considered the first onset of illness. The requirement for early onset diagnosis is not usually relevant for low and middle income countries where care seeking behaviour is poor, and thus the babies are brought to the hospital when the disease process has already progressed to a severe state.

We also observed that case definition for sepsis differed from study to study. In majority of the studies, sepsis was defined based on clinical algorithm, which also varied from study to study. Furthermore, there were studies where only culture-proved cases were considered as sepsis. This is a challenging issue: if we consider all clinically suspected sepsis cases as true, we run the risk of diluting true sepsis cases; if not, then we are possibly missing out the actual infections which are not captured by blood culture.

Additionally, >90% of biomarker studies were from developed countries, and >50% were specifically from Europe. Therefore, there is almost no data from developing countries where the populations are different with respect to their exposure to microbes, aetiology of infection, nutritional status, time for care-seeking behaviour, and other factors.

In conclusion, biomarker research has many limitations, its progress has slowed down and research results are far from reaching the population where biomarkers are needed most.

Several steps are needed to facilitate the uptake of biomarkers as tools to diagnose neonatal infections in the developing countries; i) a multi-country and multi-site study using a harmonized protocol to detect the most promising biomarkers, ii) formulation of their use in single and/or multiplex format, iii) development of point care device and their trial in the facility level and iv) validation of point of care device in large population based sites of multiple countries.



Acknowledgment: We thank Maksuda Islam for administrative support. We also acknowledge support from the principal grant holder, Prof. Igor Rudan from the University of Edinburgh, for financial support and technical guidance.

Funding: Bill and Melinda Gates Foundation.

Ethical approval: Not required.

Authorship declaration: MSI and SKS conceived and designed the study and developed the protocol. MMe JKM, RM, MMo and SKS conducted the literature review and analysis. MMe and SKS participated in writing and revision 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) and declare support from Bill and Melinda Gates Foundation for the submitted work. The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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PAPERS

Emerging biomarkers for the diagnosis of severe neonatal infections applicable to low-resource settings

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More than 500 000 children die each year in low resource settings due to serious neonatal infections. Better diagnostics that can be utilized in these settings to identify infected infants has the potential to significantly reduce neonatal deaths and the associated morbidity. A systematic review was performed and identified more than 250 potential new biomarkers for the diagnosis of serious neonatal infections. Eight of these biomarkers were both high-performance and high-abundance (antithrombin, inter-α inhibitor proteins, interferon-γ inducible protein-10, interleukin-1 receptor antagonist, LPS binding protein, mannose binding lectin, serum amyloid A, resistin, visfatin), and are promising for the diagnosis of serious neonatal infections in low resource settings. Future clinical trials comparing these biomarkers with more traditional biomarkers seem warranted.

Reducing global childhood mortality by two-thirds is a Millennium Development Goal of the United Nations. Severe neonatal infections are one of the most significant causes of pediatric mortality, resulting in more than 500 000 deaths each year (1). 99% of these deaths occur in low resource settings (2). Identifying neonates with severe infections is difficult in high resource settings, and limited laboratory capability in low resource settings makes diagnosis even more challenging. Clinical criteria for the diagnosis of neonatal 'sepsis' have been developed and are included in the WHO Integrated Management of Childhood Illness (IMCI) program (3). In one large multicenter study of neonates seeking medical attention in low resource settings, the ICMI guidelines were 85% sensitive and 75% specific (4). There are increasing efforts to have community health care workers visit all newborns and implement interventions according to IMCI guidelines (5). As more neonates are screened for severe neonatal infections, the predictive value of the clinical guidelines would be expected to decrease, resulting in a much larger percentage of misdiagnoses, with significant associated mortality, cost, and complications. Inexpensive point-of-care testing that could increase the performance (both sensitivity and specificity) of these diagnostic algorithms has the potential to substantially improve the global management of severe neonatal infections.

This review sought to identify promising new biomarkers for the diagnosis of serious neonatal infections, characterize the biomarkers with the

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greatest potential utility in low resource settings, and help prioritize biomarkers that warrant further research and/or development. We focused on the performance of soluble biomarkers and combined biomarkers. Hundreds of biomarkers were identified that have been associated with 'sepsis' or predicted to be good biomarkers for sepsis. This review focused exclusively on biomarkers with published performance data for the diagnosis of serious neonatal infections. New biomarkers whose performance appears to have the potential to outperform existing biomarkers are highlighted. Because there are theoretical benefits to combined biomarkers, and because combined biomarkers are becoming increasingly feasible in less expensive point-of-care formats, additional effort was made to identify the performance of biomarker combinations.

METHODS

Literature review strategy

This search was focused on identifying 'emerging' soluble host response biomarkers for the diagnosis of serious newborn infections. Biomarkers for the diagnosis of serious newborn infections that have been studied extensively in high resource settings such as procalcitonin (PCT), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-6 (IL-6), and interleukin(IL-8), have been reviewed elsewhere (6–8) and were not the focus of this review, unless they were included in a combined biomarker panel. Several different strategies were utilized to identify a broad list of potential biomarkers for the diagnosis of serious neonatal infections (**Figure 1**). First, Pubmed was queried for "neonatal OR infant", "sepsis OR infection", and "biomarker." The search was restricted to reviews in English, which identified 119 abstracts. Ninety-four abstracts were focused exclusively on existing biomarkers. Thirteen review articles were relevant to novel or emerging biomarkers, and reviewed in detail to identify potential biomarkers for severe neonatal infections (6,7,9–19). Second, more relaxed searches not restricted to neonates or infants, or not restricted to reviews, but published within the last two years, were also performed in an effort to identify emerging biomarkers, e.g. references (20–31). Third, a non-exhaustive search of US patent and patent applications using www.uspto.gov and www.google.com/patents using "sepsis" and "diagnosis" identified other potential biomarkers, e.g. references (32,33). This combined search strategy identified 282 potential biomarkers. Starting with this broad list of potential biomarkers, Pubmed was searched to identify original research articles regarding each of these biomarkers. Thirty-three studies provided diagnostic performance data in infant populations (20,24,30,34–63).

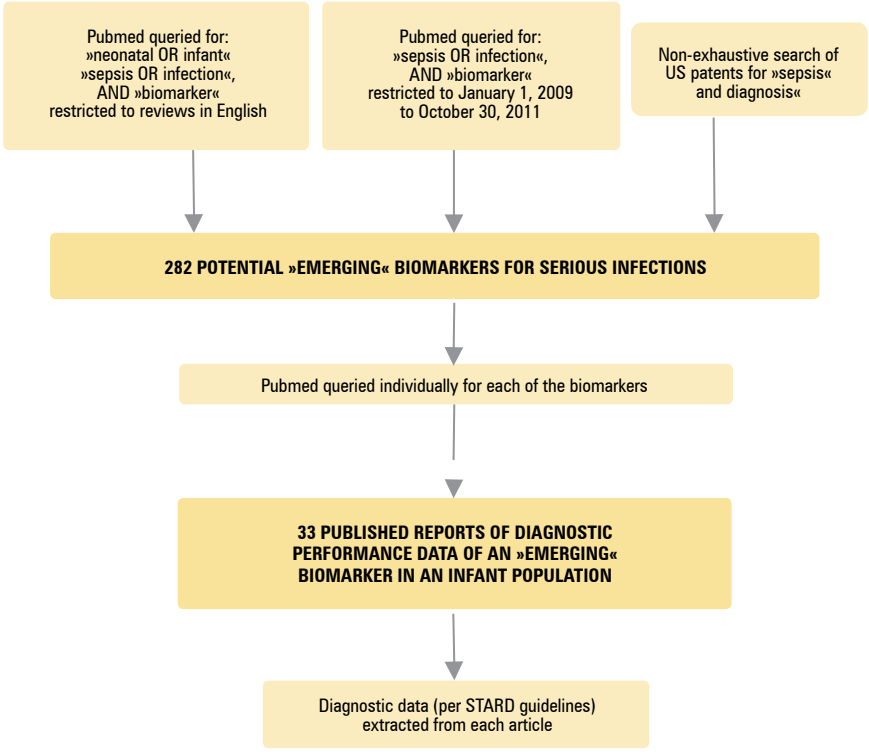


Figure 1 Strategy used to identify individual »emerging« biomarkers for the diagnosis of serious neonatal infections. Procalcitonin, C-reactive protein, tumor necrosis factor-α, interferon-α, interleukin-6, and interleukin-8, were considered »established« biomarkers and were not reviewed.

Pubmed was also queried for "neonatal OR infant", "sepsis OR infection", and "combination biomarker" to identify 19 studies that evaluated the performance of combinations of biomarkers for the detection of serious newborn infections (25,29,35,51,52,57,64–79). When necessary, corresponding authors were contacted to clarify aspects of the respective studies.

Data collected

Positive predictive value (PPV) and negative predictive value (NPV) were felt to be clinically relevant metrics but were hard to compare across studies in which disease prevalence differed. Sensitivity and specificity are independent of disease prevalence and easier to compare across studies. Area under curve (AUC) of the receiver operator characteristic (ROC) curve is a widely used summary measure of diagnostic assay performance (80). Data on these performance parameters was collected when present or when it could be calculated from the published data. Standards for Reporting of Diagnostic Accuracy (STARD) represent expert opinion regarding 25 items that should be included in diagnostic literature (81). Data on these performance characteristics was collected if available.

Biomarker performance characteristics of interest for low resource settings

In order to help identify biomarkers that would improve the performance over existing clinical algorithms, performance data was considered promising if sensitivity or specificity was greater than 90%, and/or AUC >0.9. Technical features of the assay applicable to implementation in low resource settings were also evaluated. Specifically, we sought biomarkers that appeared promising for adaptation to low cost point-of-care formats. Turn-around time of less than two hours and the ability to perform the test without laboratory infrastructure have been considered essential features

Table 1 Acute phase reactant biomarkers for neonatal sepsis

Biomarker Name	Sample size(n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off level	LOD	ROC (AUC)	Assay method	Reference
Serum Amyloid A (SAA)	192	24	93	67	67	1 mg/mL	Not given	0.61	Automated immunoassay	51
	163	76.4	100	100	58	6.8mg/100mL	6.8mg/100mL	0.88	Immune-nephlometric assay	58
	134	96 (0 hr) 96 (24 hr)	95 (0 hr) 98 (24 hr)	85 (0 hr) 92 (24 hr)	99 (0 hr) 99 (24 hr)	8mg/L (0 hr) 10mg/L (24 hr)	0 to 386 µg/mL	0.99 (0 hr) 0.99 (24 hr)	Latex photometric immunoassay	61
	116	95 (0 hr) 100 (8 hr) 97 (24 hr)	93 (0 hr) 85 (8 hr) 77 (24 hr)	87 (0 hr) 76 (8 hr) 67 (24 hr)	97 (0 hr) 100 (8 hr) 98 (24 hr)	10 µg/mL	Not given	0.81 (0 hr) 0.81 (8 hr)	ELISA	59
	94	100	93	96	Not given	10 µg/mL	Not given	Not given	ELISA	60
	40	Not given	Not given	Not given	Not given	N/A	4ng/mL	0.94	ELISA	57
	46	98	92	90	98	41.3mg/L	Not given	0.98	Nephlometry	62
LPS Binding Protein (LBP)	140	80	55	Not given	Not given	26.6 µg/mL	0.2 µg/mL	0.82	Chemiluminescent immunoassay	41
	46	82 (0 hr) 85 (24 hr)	86 (0 hr) 86 (24 hr)	65 (0 hr) 66 (24 hr)	94 (0 hr) 95 (24 hr)	11.4mg/L (0 hr) 17.2mg/L (24hr)	0.2mg/L	0.86 (0 hr) 0.91 (24 hr)	Chemiluminescent immunoassay	42
	96	100 (age<48hr) 92 (age>48hr)	94 (age<48hr) 89 (age>48hr)	89 (age<48hr) 66 (age>48hr)	100 (age<48hr) 92 (age>48hr)	21.5 mg/L (age<48hr) 17.1 mg/L (age>48hr)	Not given	0.97 (age<48hr) 0.93 (age>48hr)	Chemiluminescent immunoassay	43
	60	97	70	37	92	12.7 mg/L	Not given	0.90	Chemiluminescent immunoassay	44
	69	not evaluated, but levels of LBP in septic neonates were significantly elevated compared to healthy neonates (median, 36.6 vs. 7.8 µg/mL)					0.45 µg/mL	Not evaluated	Enzyme immunoassay	45
Inter-alpha Inhibitor Proteins (IαIp)	573	90	99	95	98	177 mg/L	50 mg/L	0.94	ELISA	46
	135	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	100 mg/L	Not evaluated	ELISA	47
Antithrombin (AT)	60	Not evaluated, but antithrombin functional levels were in septic neonates were significantly decreased compared to controls (mean, 34.87% vs. 90.5%, p<0.001)					Not given	Not evaluated	ELISA	48
	150	Not evaluated, but antithrombin functional levels in septic neonates were significantly lower than controls					Not given	Not evaluated	Colorimetric assay	49
	58	92	62	60	93	15 mg/dL	Not given	Not given	Not given	50
Soluble E-selectin	192	55	82	67	74	132 ng/mL	0.009 ng/mL	0.72	ELISA	51
	120	59	87	81	69	130 ng/mL	0.5 ng/mL	0.8	ELISA	52
	108	Not evaluated				Not given	Not given	Not evaluated	Antibody microarray	20
Plasma Fibronectin (pFN)	65	100	87.5	Not given	Not given	90 µg/mL for preterm 100 µg/mL for term	Not given	Not given	ELISA	53
	58	74	74	58	85	Not given	Not given	Not given	Not given	54
	220	75	63	11	98	120 µg/mL (age <34 wk) 145 µg/mL (age >34 wk)	Not given	Not given	ELISA	55
Mannose Binding Lectin (MBL)	97	96.7	97.1	98.3	94.4	0.5 µg/mL	0.075 µg/mL	Not given	Immunoassay	30

PPV – positive predictive value, NPV – negative predictive value, ROC (AUC) – receiver operator curve (area under the curve), LOD – lower limit of detection, ELISA – enzyme-linked immunosorbent assay

for implementation in the lowest resource settings (82). Currently, lateral flow immunoassays are the primary diagnostic format that meets these criteria. Lateral flow immunoassays in widespread clinical use generally have a lower limit of detection (LOD) of 1ng/mL, although newer methods, such as a europium-based lateral flow assay with a LOD of 0.3ng/mL, have been reported (83). None of the new biomarkers described in this review were tested in a lateral flow format, but we focused on relatively high abundance biomarkers (≥1ng/mL), that could theoretically be adapted to a lateral flow format with existing technology. Because the precision of inexpensive lateral flow tests is usually decreased, good discrimination between the limit of detection and the diagnostic cut-off was also considered important for assay performance. Testing cord blood was felt to be impractical on a large scale in low resource settings, and performance data on biomarkers that were only tested on cord blood were not included. Other characteristics of the biomarker that seemed to have potential to impact their use in low resource settings were also noted.

RESULTS

Summary of biomarkers identified

In recent years, genomic and proteomic technology has identified numerous gene transcripts and proteins associated with 'sepsis', and increasing understanding of immune responses has led to many proposed biomarkers for sepsis. The majority of these biomarkers have not been evaluated as diagnostics, and only a few of those have been studied in children. We were able to identify infant diagnostic performance data on 23 biomarkers. Seven of these biomarkers were acute phase reactants: (serum amyloid A (SAA) (19,51,58–62), LPS binding protein (LBP) (41–45), inter-α inhibitor proteins (IαIp) (46,47), antithrombin (AT) (48–50), and soluble E-selectin (20,51,52), plasma fibronectin (pFN) (52–54), and mannose binding lectin (MBL) (30) (**Table 1**).

Fourteen cytokine biomarkers were identified, including six pro-inflammatory cytokines: (interleukin-1α (IL-1α)

Table 2 Emerging cytokine and chemokine biomarkers for neonatal sepsis

		Biomarker name	Sample size	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off	LOD	ROC (AUC)	Assay method	Reference
CYTOKINES	Pro-inflammatory	Interleukin-1α (IL–1α)	62	83	88	77	92	12 pg/mL	1 pg/mL	Not given	ELISA	34
		Interleukin-1β (IL–1β)	155	50	63	25	76	3.7 pg/mL	7.2 pg/mL	0.57	Cytometric bead assay	35
			164	11	97	40	87	90 pg/mL	Not given	0.61	Cytometric bead assay	36
		Interleukin-12p70 (IL–12p70)	155	64	56	36	80	2.7 pg/mL	1.9 pg/mL	0.62	Cytometric bead assay	35
			164	28	98	71	89	75 pg/mL	Not given	0.74	Cytometric bead assay	36
		Interleukin-18 (IL-18)	84	Not available, IL-18 levels increased in septic neonates vs. neonates with necrotizing enterocolitis				Not given	12.5 pg/mL	Not given	ELISA	37
			108	Not evaluated, but IL-18 levels were highly associated with sepsis				Not given	Not given	Not given	ELISA	20
		Granulocyte colony stimulating factor (G-CSF)	171	95	73	40	99	200pg/mL	10 pg/mL		ELISA	38
			254	57	95	86	82	950 pg/mL	Not given	0.8	ELISA	39
		Resistin	105	93	95	Not given	Not given	8 ng/mL	1.85 ng/mL	0.91	EIA	24
		Visfatin	105	92	94	Not given	Not given	10 ng/mL	Not given	0.92	EIA	24
	Anti-inflammatory	Interleukin-10 (IL-10)	155	84	84	67	93	7.6 pg/mL	3.3 pg/mL	0.90	Cytometric bead assay	35
		Inteleukin 1 receptor antagonist (IL-1ra)	101	93	92	Not given	Not given	11 000 pg/mL	440 pg/mL	0.94	2-step ELISA	40
			254	33	89	80	82	Not given	Not given	0.73	ELISA	39
CHEMOKINES	CXC	Growth-related oncogene-α (GRO-α)	155	82	60	45	89	55 pg/mL	10 pg/mL	0.81	Cytometric bead assay	35
		Interferon-γ-inducible protein-10 (IP-10)	155	93	89	77	97	1250 pg/mL	2.8 pg/mL	0.95	Cytometric bead assay	35
			60	81	95	Not given	Not given	48 pg/mL	1.67 pg/mL	0.84	ELISA	63
		Monokine induced by IFN-γ (MIG)	155	80	78	59	91	650 pg/mL	2.5 pg/mL	0.84	Cytometric bead assay	35
	CC	Regulated upon Activation Normal T cells Expressed and Secreted (RANTES)	155	86	45	38	89	11800 pg/mL	10 pg/mL	0.67	Cytometric bead assay	35
		Monocyte chemoattractant protein 1 (MCP-1)	155	68	68	46	84	357 pg/mL	2.7 pg/mL	0.78	Cytometric bead assay	35

PPV – positive predictive value, NPV – negative predictive value, ROC (AUC) – receiver operator curve (area under the curve), LOD – lower limit of detection, ELISA – enzyme-linked immunosorbent assay, EIA – enzyme immunoassay

Table 3 Diagnostic performance of other biomarkers for neonatal sepsis

Biomarker name	Sample size (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off	LOD	ROC (AUC)	Assay method	Reference
Soluble intercellular adhesion molecule 1 (sICAM-1)	149	77	76	67	84	228 ng/mL	0.096 ng/mL	0.79	ELISA	51
	43	88	86	75	94	300 ng/mL	Not given	Not given	Not given	56
Apolipoprotein C2 (ApoC2)	80	Not evaluated				Not given	0.3 ng/mL	0.79	Mass spectrometry and ELISA	57

PPV – positive predictive value, NPV – negative predictive value, ROC (AUC) – receiver operator curve (area under the curve), LOD – lower limit of detection, ELISA – enzyme-linked immunosorbent assay

(34), interleukin-1β (IL-1β) (35,36), interleukin-12p70 (IL-12p70) (35,36), interleukin-18 (IL-18) (20,37), granulocyte colony stimulating factor (G-CSF) (38,39), and resistin (24); two anti-inflammatory cytokines – interleukin-10 (IL-10) (73) and interleukin-1 receptor antagonist (IL-1ra) (39,40); one probable cytokine – visfatin (24); and five chemokines – growth-related oncogene α (GRO-a) (35), interferon-γ-inducible protein 10 (IP-10) (35,84), monokine induced by interferon-γ (MIG) (35), Regulated upon Activation Normal T cells Expressed and Secreted (RANTES) (35), and monocyte chemoattractant 1 (MCP-1) (35) (**Table 2**).

One soluble cell surface marker, soluble intercellular adhesion molecule-1 (sICAM-1) (51,56) and one molecule involved in triglyceride metabolism, apolipoprotein CII (ApoC2) (57) were also identified (**Table 3**). Although no absolute performance data is available for interleukin-18 (IL-18), it was included based on the strength of performance data relative to other biomarkers (20,37).

Summary of individual biomarker performance

For the 23 soluble biomarkers with published diagnostic performance data in infant populations, the available data regarding sensitivity, specificity, PPV, NPV, and area under receiver operator curves is summarized in **Tables 1–3**. The collective performance of these biomarkers varied widely: sensitivity from 11–100%, specificity from 45–98%, PPV from 35–96%, NPV 66–98%, and area under the receiver operator curve of 0.57–0.95. There was often significant variability in the performance of individual biomarkers when evaluated in separate studies. To assess the technological feasibility of these assays in low resource settings, assay method, limit of detection, and cut-off concentration were also recorded. All of the soluble biomarkers were measured by immunoassay, most by enzyme linked immunossorbent assays, although some newer studies were done with cytometric bead assays and/or using chemiluminesence. One study used an unbiased proteomics approach to identify promising biomarkers that were then quantified by immunoassay (57). None of these assays were performed in a point-of-care format. The cut-off concentrations used for the cytokine biomarkers (2.7 pg/mL–12 ng/mL) were orders of magnitude lower than the acute phase reactants (130 ng/mL–177 mg/mL).

Most promising individual biomarkers

Despite the limitations of the data, nine soluble biomarkers (IL-1ra, IP-10, SAA, LBP, IαIp, resistin, visfatin, MBL, and AT) emerged as promising individual candidates for further study (**Table 4**).

IL-1ra and IP-10 are both inflammatory cytokines that are elevated early in infection (85,86). The best reported sensitivity of IL-1ra (100%) is promising but the range of reported sensitivities (33–100%) is concerning. IL-1ra has a short half-life of 4 to 6 hours (87) which may explain the variability in sensitivity and could be a limitation for general use as a stand-alone biomarker for severe neonatal infections. Studies of IP-10 have shown moderate sensitivity (81–93%) despite significant difference in cut-off concentrations (1.2–48 ng/mL). One study demonstrated an excellent AUC (0.95), which may be the single most important performance parameter. The immune physiology of IP-10 is also attractive because although it is a chemokine it is interferon-induced like other acute phase reactants, with the potential benefit of assessing different aspects of the immune response.

The physiologic roles of resistin and visfatin are less well characterized. Resistin was initially described as an adipocyte-secreted peptide (adipokine) but is now known to be secreted by monocytes and to be a more general pro-inflammatory cytokine (88). Visfatin was also initially described as an adipokine and an insulin mimetic. However, visfatin is also known as pre-B cell colony-enhancing factor (PBEF), which is a cytokine that is increased in a variety of inflammatory conditions and can induce cellular expression of other pro-inflammatory cytokines, such as TNF-a, IL-1β, and IL-6 (89). In one report, both molecules performed well as biomarkers for serious newborn infections, with sensitivity and specificity greater than 90%. The cut-offs of 8 ng/mL and 10 ng/mL respectively, should be easily achievable in a lateral flow format (24). Despite the relatively limited amount of performance data these molecules appear promising and seem to warrant further study.

Table 4 Diagnostic performance of the most promising biomarkers for neonatal sepsis

Biomarker name	Class	Assay method	No. of neonatal studies	Median study size (range)	Median sensitivity (range)	Median specificity (range)	Median PPV (range)	Median NPV (range)	Median AUC (range)	Median cut-off (range)	References
IL-1ra	Cytokine	2-step ELISA or ELISA	2	176 (101–254)	63 (33–93)	91 (89–92)	80	82	0.84 (0.73–0.94)	11.5 ng/mL (11–12 ng/mL)	39,40
IP-10	Chemokine	ELISA or cytometric bead assay	2	108 (60–155)	87 (81–93)	92 (89–95)	77	97	0.95	0.649 ng/mL (0.048–1.25 ng/mL)	35,63
Resistin	Adipocytokine	EIA	1	105	93	95	Not given	Not given	0.91	8 ng/mL	24
Visfatin	Adipocytokine	EIA	1	105	92	94	Not given	Not given	0.92	10 ng/mL	24
SAA	Acute phase reactant	Latex agglutination or ELISA	7	104 (40–192)	96 (24–100)	93 (92–100)	89 (67–100)	97 (58–99)	0.91 (0.61–0.99)	25.7 μg/mL (8–1000 μg/mL)	51,57–62
LBP	Acute phase reactant	Chemiluminescence or enzyme or immunoassay	4	65 (46–140)	92 (80–100)	86 (55–94)	66 (37–80)	96 (92–100)	0.90 (0.82–0.97)	17.1 μg/mL (11.4–26.6 μg/mL)	41–44
IαIp	Acute phase reactant	ELISA	1	573	90	99	95	98	0.94	177 μg/mL	46
MBL	Innate pattern recognition	Immunoassay	1	97	97	97	98	94	Not given	0.5 μg/mL	30
AT	Anticoagulation	Not given	1	92	92	62	60	93	Not given	150μg/mL	50

IL-1ra – interleukin (IL)-1 receptor antagonist, IP-10 – interferon γ-induced protein 10, SAA – serum amyloid A, LBP – lipopolysaccharide-binding protein, IαIp – inter-alpha inhibitor protein, MBL – mannose-binding lectin, AT – antithrombin, PPV – positive predictive value, NPV – negative predictive value, ROC (AUC) – receiver operator curve (area under the curve), ELISA – enzyme-linked immunosorbent assay

The five remaining promising biomarkers are all acute phase reactants (SAA, LBP, IαIp, MBL, AT). Acute phase reactants are attractive biomarkers for severe neonatal infections because they are usually produced in large quantities by the liver for a relatively long duration. This makes them easier to quantify and provides a wider time window during which they are useful as biomarkers. Because their production is regulated by the cytokine response, the acute phase reactants tend to be produced slightly later in the course of infection (90). Therefore, compared to cytokines, acute phase reactants may be less effective diagnostic biomarkers at earlier stages of infection.

Serum amyloid A (SAA) is probably the single most promising biomarker. SAA performed extremely well in four studies published by three different groups (57,60–62) (sensitivity 96–100%, and ROC AUC of 0.94–0.997), and performed reasonably well in a fifth study, with a sensitivity of 76% and a ROC AUC of 0.875 (58). In contrast to these five studies, one study showed relatively poor performance with a sensitivity of 24%, and ROC AUC 0.61, although the specificity was 93% (51). The cut-offs used in these studies varied considerably, from 0.8 mg/L to 1000 mg/L. However, the three studies that used a cutoff of 50mg/L or less showed good sensitivity. The study by Ng et al (57) also showed good performance, and although they did not report a specific cut-off for SAA, based on the range of values in the septic children versus controls a cut-off between 11–15mg/L would have had no overlap between SD of the two populations. This data suggests that SAA is a robust biomarker for the diagnosis of serious newborn infections, although the cut-off concentration is critical for its diagnostic performance.

Despite its name, LBP is elevated in both gram-negative and gram-positive infections, and has at least moderate sensitivity (80–100%), as reported by multiple groups (41,43–45). IαIp also performed relatively well (sensitivity 90%) in the largest study (n=573), which was well-designed and prospective (46). The NPV was 97%, which may be an important performance characteristic if the biomarker is used as a screening test for severe neonatal infections. Mannose-binding lectin (MBL) is also a promising biomarker. MBL plays an important pattern recognition role in the innate immune response to pathogens, triggering the eponymous MBL pathway to complement cascade activation (91). In one recent study (30) MBL had a sensitivity of 97% and specificity of 97% for the diagnosis of septic preterm and term neonates. Antithrombin (AT) is another molecule that seems to have potential as a biomarker for serious neonatal infections. AT has anticoagulant activity and is consumed during serious infections (49). AT has been associated with sepsis in three studies (48–50), and performed reasonably well in the one study which reported diagnostic performance, with a sensitivity of 92% and a NPV of 93%, although the specificity was only 62% (50). IαIp, MBL, and AT are noteworthy because they decrease during infection, which makes them potentially very attractive to use in combination with other biomarkers that increase during infection.

Two other biomarkers seem intriguing and may have potential utility in the diagnosis of serious neonatal infections, and therefore seem worth noting. G-CSF is a key cytokine in the canonical neutrophil response to severe bacterial infections that should rise before more classical markers of infection (e.g. white blood cell and band counts), making it a logical potential biomarker for early detection of infection (92). While G-CSF did perform reasonably well in two studies, it is present at relatively low concentrations (<1 ng/mL), making adaptation to a point-of-care format challenging. ApoC2 was originally associated with preterm sepsis in a study by Rovamo et al in 1984 (93) and was more recently identified by Ng et al (56) in an unbiased proteomic screen as a potential biomarker of severe neonatal infections. ApoC2 is synthesized by the liver and is involved in triglyceride synthesis,

Table 5 Diagnostic performance of combination biomarkers

Biomarker(s)	Sample size (n)	Notes	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off value	Reference
CRP	192	*reported for culture positive cases	80	71	43	93	0.4mg/L	51
CRP+sICAM-1, SAA, and sE-selectin			85	67	94	41	0.4mg/L, 249ng/mL, 1mg/L, 132mg/L	
CRP+ sICAM-1			72	75	44	91	0.4mg/L, 249ng/mL	
CRP		*reported for culture positive and culture negative, clinically suspected sepsis cases	69	70	60	79	0.4mg/L	
CRP+sICAM-1, SAA, and sE-selectin			90	67	64	91	0.4mg/L, 228ng/mL, 1mg/L, 132mg/L	
CRP+ sICAM-1			79	76	68	85	0.4mg/L, 228ng.mL	
sTREM-1	52		70	71	62	78	144pg/mL	75
IL-6			80	81	74	86	66pg/mL	
sTREM-1 + IL-6			90	62	81	77	144pg/mL, 66pg/mL	
PCT	98		65	60	52	59	63.4 pg/mL	77
IL-10			92	84	80	89	17.3 pg/mL	
nCD64			92	71	69	83	2.6%	
IL-10 + nCD64			95	83	79	86	17.3 pg/mL, 2.6%	
PCT + IL-10			75	68	53	64	36.4 pg/mL, 17.3 pg/mL	
PCT + nCD-64			78	64	58	69	36.4 pg/mL, 2.6%	
ApoC2/SAA	104	*at day 0	96	76	82	95	0.199	57
		*day 0 and day 1	100	61	75	100	0.199	
CRP	120		86	97	96	88	8 mg/L	52
sE-selectin			59	87	81	69	130 ng/mL	
CRP + sE-selectin			45	100	100	65	8 mg/L, 130 ng/mL	
PCT	123		21	92	46	79	25 ng/mL	64
			69	67	39	87	5.75 ng/mL	
IL-6			57	94	76	88	250 pg/mL	
			71	71	43	89	12 pg/mL	
PCT + IL-6			71	88	65	91	25ng/mL, 250 pg/mL	
IP-10	155		93	89	77	97	1250 pg/mL	35
IP-10 +IL-6			98	72	58	99	1250 pg/mL, 26.1 pg/mL	
IP-10 + IL-6 + IL-10			98	61	50	99	1250 pg/mL, 26.1 pg/mL, 7.6 pg/mL	
IP-10 + IL-10			98	76	61	99	1250 pg/mL, 7.6 pg/mL	
IP-10 + GRO-α			96	58	47	97	1250 pg/mL, 55 pg/mL	
IP-10 + GRO-α +IL-8			100	39	39	100	1250 pg/mL, 55 pg/mL, 62 pg/mL	
IP-10 + IL-8			98	53	45	98	1250 pg.mL, 62 pg/mL	
IP-10 + IL-8 + MIG			98	44	41	98	1250 pg.mL, 62 pg/mL, 650 pg/mL	
IP-10 + MIG			93	76	60	97	1250 pg/mL, 650 pg/mL	
IP-10 + GRO-α + IL-10			98	51	44	98	1250 pg/mL, 55pg/mL, 7.6pg/mL	
IP-10 + GRO-α + MIG			96	47	42	96	1250 pg/mL, 55 pg/mL, 650 pg/mL	
CRP	77		96	89	79	98	5 mg/L	70
IL-6			35	93	67	76	150 pg/mL	
CRP + IL-6			35	100	100	78	5 mg/L, 150 pg/mL	
CRP and/or IL-6			96	82	69	98	5 mg/L, 150 pg/mL	
CRP	111		65	52	63	54	14 mg/L	76
CRP + IL-6			92	41	67	80	14 mg/L, 60 pg/mL	
CRP + IL-8			97	41	68	92	14 mg/L, 50 pg/mL	
CRP	1291		54			86	10 mg/L	68
IL-8			44	90	58	83	70 pg/mL	
CRP + IL-8			80	87	68	93	10 mg/L, 70pg/mL	
CRP	359	*at 0 hours	49	91	73	77	10 mg/L	67
CD64			79	89	78	89	6136 antibody-PE molecules bound/cell	
CRP + CD64			81	82	69	89	10 mg/L, 6136 antibody-PE molecules bound/cell	
CRP		*at 24 hours	60	83	64	80	10 mg/L	
CD64			96	81	71	97	6136 antibody-PE molecules bound/cell	
CRP + CD64			97	71	73	98	10 mg/L, 6136 antibody-PE molecules bound/cell	
CRP	105	*at 0 hours	69	96	93	80	10 mg/dL	71
IL-6			76	73	67	81	18 pg/mL	
IL-8			75	66	60	80	100 pg/mL	
CRP + IL-6			89	73	70	90	10 mg/dL, 18 pg/mL	
CRP + IL-8			89	66	65	90	10 mg/dL, 100 pg/mL	

CRP – C-reactive protein, IL – interleukin, sICAM-1 – soluble intercellular adhesion molecule-1, SAA – serum amyloid A, IL-12p70 – IL-12 protein 70, sTREM-1 – soluble triggering receptor expressed on myeloid cells, ApoC2 – apolipoprotein C-II, GRO-α – growth-related oncogene-α, MIG – monokine induced by interferon γ, PCT – procalcitonin, TNF – tumor necrosis factor, PPV – positive predictive value, NPV – negative predictive value, PE – phycoerythrin

Table 5 – continued Diagnostic performance of combination biomarkers

Biomarker(s)	Sample size (n)	Notes	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off value	Reference
CRP		*at 24 hours	78	94	91	83	10 mg/dL	
IL-6			63	76	74	66	18 pg/mL	
IL-8			49	79	71	59	100 pg/mL	
CRP + IL-6			83	78	75	84	10 mg/dL, 18 pg/mL	
CRP + IL-8			76	79	79	83	10 mg/dL, 100 pg/mL	
CRP	76		49	100	100	58	8 mg/L	78
PCT			77	91	93	72	6 ng/mL	
PCT + CRP			83				8 mg/L	
PCT + IL-6			89				8 mg/L	
CRP	60		80	92			1.52 mg/dL	74
CRP + IL-8 + sReceptor IL-2			85	97			1.52 mg/dL, 63 pg/mL, 2780U/mL	
CRP	110	*at 0 hours	65	99	96	87	12 mg/L	73
IL-6			78	92	81	91	31 pg/mL	
CD64			95	88	80	97	4000 PE molecules bound/cell	
CRP		*at 24 hours	72	100	100	90	12 mg/L	
IL-6			44	93	72	81	31 pg/mL	
CD64			97	90	80	99	4000 PE molecules bound/cell	
CRP(0 hr) + IL-6(0 hr) + CD64(24 hr)			100	86	74	100	12 mg/L, 31 pg/mL, 4000 PE molecules bound/cell	
CRP	166		63	89			10 mg/L	66
IL-6			78	64			20 pg/mL	
CRP +/or IL-6			96	58			10 mg/mL, 20 pg/mL	
CRP	90		69	86	84	73	5 mg/L	69
sICAM-1			78	90	90	80	300µg/mL	
CRP + sICAM-1			93	80	82	92	5 mg/L, 300µg/mL	
CRP	101		60	100	100	75	12 mg/L	79
IL-6			89	96	95	91	31 pg/mL	
TNF-α			82	86	82	85	17 pg/mL	
CRP + IL-6			93	95	95	95	12 mg/L, 31 pg/mL	
CRP + TNF-α			91	86	84	92	12 mg/L, 17 pg/mL	
IL-6 + TNF-α			95	84	83	96	31 pg/mL, 17 pg/mL	
CRP + IL-6 + TNF-α			95	84	82	96	12 mg/L, 31 pg/mL, 17 pg/mL	
IL-6	55		80	78			500 pg/mL	65
TNF-α			73	94			70 pg/mL	
IL-6 + TNF-α			60	100			500 pg/mL, 70 pg/mL	

CRP – C-reactive protein, IL – interleukin, sICAM -1 – soluble intercellular adhesion molecule-1, SAA – serum amyloid A, IL-12p70 – IL-12 protein 70, sTREM-1 – soluble triggering receptor expressed on myeloid cells, ApoC2 – apolipoprotein C-II, GRO-α – growth-related oncogene-α, MIG – monokine induced by interferon γ, PCT – procalcitonin, TNF – tumor necrosis factor, PPV – positive predictive value, NPV – negative predictive value, PE – phycoerythrin

but its role in infection remains speculative. In the validation phase of the study by Ng et al (57), ApoC2 did not perform well alone (ROC curve area 0.79), but was identified through logistic regression as an optimal biomarker when combined with SAA (ROC curve area 0.96).

Combination biomarkers

Currently available analyses of combination biomarkers have been rudimentary and have had mixed results (35,51,52,57,64–79). One exception was the recent study by Ng et al (57) which had a more sophisticated proteomic-based biomarker discovery phase, followed by logistic regression to identify optimal biomarker combinations, and performance was validated in a separate cohort. **Table 5** summarizes data about the performance of combination biomarkers. The majority of these studies have evaluated biomarkers in combination with CRP because CRP is already in widespread clinical use for the diagnosis of infection. CRP is less useful in the earliest phases of severe neonatal infection because it is an acute phase reactant and does not peak until 12 to 24 hours after infection and can also be triggered by non-infectious insult such as trauma (68). Recent studies have shown that the diagnostic performance of CRP may be improved upon when used in combination with other acute phase reactants and early mediators of inflammation. A study by Dollner et al (66) compared the diagnostic performance of CRP, IL-6, soluble tumor necrosis factor p55 and p75, sICAM-1 and soluble (s) E-selectin. CRP was the best single test with a sensitivity of 70% and specificity of 90%, but sensitivity or specificity could be improved when combined with IL-6. Another study that evaluated levels of sICAM-1, sE-selectin and SAA in combination with CRP found that combining all four biomarkers increased sensitivity from 70% for CRP alone to 90%, but specificity remained low at 67% (51). Hansen et al observed that the sensitivity and NPV of CRP were significantly improved when combined with sICAM-1 levels. In neonates under 5 days old, sensitivity increased

from 69% to 93% and NPV increased from 73% to 92% (68). Not all studies have demonstrated improved diagnostic utility when biomarkers are combined. Resch et al evaluated the reliability of procalcitonin (PCT), Interleukin-6 (IL-6) and CRP to diagnose early onset neonatal sepsis and found that combining the best performing marker, PCT, with either IL-6 or CRP did not increase the sensitivity for diagnosing sepsis compared to using PCT alone (78).

Luminex, mass spectrometry, and other highly multiplexed detection methods have allowed for increased screening of biomarker combinations in the last several years. In a 2007 study, Ng et al (35) associated elevated levels of interferon-γ-inducible protein 10 (IP-10) with neonatal sepsis. As mentioned earlier, using IP-10 levels alone resulted in a sensitivity and specificity of 93% and 89%, respectively, with a NPV of 97%. When IP-10 concentration was combined with various other markers of infection such as IL-6, IL-8, and IL-10, the sensitivity and NPV were slightly improved by up to 7%, but the specificity and PPV were dramatically decreased by up to 50% (35). In 2010 Ng et al (57) reported an unbiased, mass spectrometry-based, proteomic approach to identify biomarkers that were specifically associated with acute neonatal sepsis and normalized after treatment. Not only did they identify a previously undescribed biomarker (Pro-apoC2), but they also used logistic regression to identify a combination of two biomarkers (Pro-apoC2 and SAA) that resulted in a test with 96% sensitivity and 76% specificity. The combined ApoSAA score had a NPV of 95% on day 0 (of suspected infection) and 100% when levels were measured on days 0 and 1. Early detection of infection based on the combined biomarkers could potentially result in a 45% reduction of antibiotic use when antibiotic therapy is withheld or discontinued in uninfected infants (57). The experimental approach used to identify this combination required advanced technology and rigorous mathematical analysis, but both biomarkers are present at relatively high levels and should be amenable to a multiplexed lateral flow format making the ApoSAA score an extremely promising combined biomarker.

A few studies report on the combined use of soluble biomarkers with flow cytometry to measure cell surface receptor expression. An early study by Ng et al (73) in 110 neonates found that combining IL-6 and CRP levels measured at 0 hours with CD64 measured at 24 hours yielded good diagnostic performance with sensitivity, specificity, PPV and NPV of 100, 86, 74, 100%. CD64 measured at 24 hours performed almost as well on its own with 97% sensitivity and 90% specificity (73). A follow-up study in 2004 by Ng et al (67) again showed improved diagnostic performance of CRP and CD64 together versus CRP alone (sensitivity increased from 49% to 81%), but the excellent performance of the earlier study was not replicated, and the performance of the combined biomarker did not outperform CD64 alone. Zeitoun et al (77) evaluated the performance of CD64 in combination with IL-10 and found that the combined biomarker had a sensitivity of 95% and specificity of 79%, but the combination did not perform significantly better than IL-10 alone. Although CD64 is promising alone or in combination, quantification requires measuring the mean fluorescent intensity of individual cells, which diminishes the feasibility of this approach in low resource settings.

DISCUSSION

This review identified at least nine biomarkers (AT, CRP, IαIp, IL-1ra, IP-10, SAA, LBP, MBL, PCT, resistin and visfatin) that appear promising for the diagnosis of serious neonatal infections in low resource settings. These biomarkers appear to have better performance than the existing clinical algorithms used in low resource settings. Furthermore, the clinical cut-off concentration used for these biomarkers were all in a range that should be detectable with lateral flow immunassays, a diagnostic technology platform that has a proven track-record in low resource settings. Especially with further study of these biomarkers in combination, there seems to be great potential to improve the diagnosis of severe neonatal infections in low resource settings.

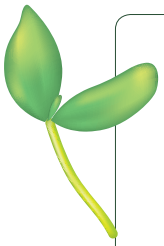
Although these emerging biomarkers are promising, there are important limitations to the current literature. All of the studies reviewed focused on severe neonatal infections, yet there was significant heterogeneity in how this population was defined. Some studies excluded premature or low birth-weight infants, the populations most vulnerable to infection. 'Neonatal' included infants ranging from birth to two months old. The definition of 'sepsis' was also quite variable, particularly in instances of suspected sepsis with negative blood cultures and whether coagulase negative staphylococcal growth in a blood culture was considered sepsis. Timing of diagnostic testing relative to the onset of symptoms was also variable. Importantly, none of these assays were tested in low-resource settings, where rates of inflammation and/or the pre-test probability of infection may be different from high resource settings. The heterogeneity of the studies makes it difficult to compare the relative performance of biomarkers across studies. Furthermore, many of the studies did not compare the performance of new biomarkers to established biomarkers (e.g. CRP), which makes their benefit relative to existing biomarkers difficult to assess. The performance data for many of the biomarkers comes from a single study, for example with IaIp, MBL, resistin, visfatin. Where multiple published reports of a marker exist, they often come from a single research group. Given the large number of biomarkers reported to be associated with 'sepsis', reporting bias is a concern. For such biomarkers, confirmation of perfor-

mance in additional studies, preferably by other research groups will be particularly important in order to help validate the performance of these biomarkers. In contrast, a few biomarkers, like SAA, LBP, and IP-10, have shown consistently good performance in several studies, and are more likely to be reliable diagnostic biomarkers.

Another potential limitation of the data is that most of the studies reviewed included relatively small numbers of participants (average population size of 135) and over-fitting of the biomarker performance is a significant concern. In almost all of the studies reviewed the diagnostic cut-off was fit to the dataset, often using receiver operator curves, and therefore likely represents the best-case performance for the biomarker. All of the reviewed biomarkers should be considered to be at the discovery phase and will need independent cross-validation to accurately evaluate their performance. One potential exception is the 2010 study by Ng et al that used a more rigorous approach, starting with unbiased proteomics to discover mass spectrometry peaks associated with sepsis, then refining that set of potential biomarkers by focusing on peaks that showed a reversal pattern after resolution of sepsis. These peaks were then identified and quantified, and logistic regression was used to identify the combination of biomarkers with the most discriminatory power. A score based on this combined biomarker was cross-validated in an independent case-control group as well as a prospective cohort (57). This robust approach is much more likely to identify biomarkers and cut-offs that are reproducible in future studies.

Despite the limitations noted above, several soluble biomarkers seem to have potential to significantly improve the diagnosis of severe neonatal infections. The number of studies reflects not only the perceived clinical need for better diagnostics but also a significant amount of work that has already been done on biomarker discovery. In contrast, less effort has been directed toward determining the optimal combinations of biomarkers and validating previously identified biomarkers. Theoretically, a combination of these biomarkers should have the best performance. However, the number of potential biomarker combinations rises exponentially, where the number of possible combinations = 2^p-1, and p is the number of biomarkers. Because the number of participants in a study should theoretically be greater than the number of biomarker combinations evaluated, much larger studies will be necessary to identify and validate combination biomarkers. This imposes practical limits on the total number of biomarkers that can be analyzed, but it seems feasible to validate 5–10 of the biomarkers identified in this review, in combination with a few of the promising traditional biomarkers. To be relevant, future studies should be conducted in low resource settings, with careful definition of 'sepsis', consideration for the amount of blood that can routinely be obtained, and designed with significant biostatistical guidance.

Severe neonatal infections are a significant cause of global mortality. Modest improvement in the diagnosis of severe neonatal infections could lead to significant decreases in infant mortality and a substantial number of lives saved. The actual impact of diagnostics depends on the availability and performance of the test, as well as the availability, uptake, and effectiveness of the treatment based on the test results. Large numbers of small studies have described hundreds of biomarkers associated with severe neonatal infections. The aim of this review was to summarize and consolidate the extensive work that has been already been done with the hope of helping to prioritize biomarkers that warrant further study. Large rigorous validation studies focusing on combinations of the most promising biomarkers (CRP, PCT, IL-1ra, IP-10, SAA, LBP, MBL, IαIp, AT, resistin, visfatin, and perhaps G-CSF and ApoC2) are necessary in order to determine their true performance characteristics and seem warranted in an effort to reduce global infant mortality.



Acknowledgments: We thank Terence C.W. Poon, PhD, at Li Ka Shing Institute of Health Sciences and The Chinese University of Hong Kong, for providing additional details regarding the study by Ng et al (ref. 47).

Funding: Support for this review was provided by the Bill and Melinda Gates Foundation.

Ethical approval: Not required.

Authorship declaration: All authors actively contributed to revising the manuscript and gave their final approval. MG and CR were responsible for study conception and design, actively supervised the project, and participated in interpretation of the data. TW, CG, SH, VS, and JP performed the literature review and participated in the interpretation of the data. TW participated in the design of the review, and drafted the manuscript. CG also contributed to drafting 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) and declare support from Bill and Melinda Gates Foundation for the submitted work. The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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journal of global health

PAPERS

Communicable disease control in China: From Mao to now

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China's progress on communicable disease control (CDC) in the 30 years after establishment of the People's Republic in 1949 is widely regarded as remarkable. Life expectancy soared by around 30 years, infant mortality plummeted and smallpox, sexually transmitted diseases and many other infections were either eliminated or decreased massively in incidence, largely as a result of CDC. By the mid-1970s, China was already undergoing the epidemiologic transition, years ahead of other nations of similar economic status. These early successes can be attributed initially to population mobilization, mass campaigns and a focus on sanitation, hygiene, clean water and clean delivery, and occurred despite political instability and slow economic progress. The 10-year Cultural Revolution from 1966 brought many hardships, but also clinical care and continuing public health programs to the masses through community-funded medical schemes and the establishment of community-based health workers. These people-focused approaches broke down with China's market reforms from 1980. Village doctors turned to private practice as community funding ceased, and the attention paid to rural public health declined. CDC relied on vertical programs, some of them successful (such as elimination of lymphatic filariasis and child immunisation), but others (such as control of schistosomiasis and tuberculosis) demonstrating only intermittent progress due to failed strategies or reliance on support by the poorest governments and health workers, who could not or would not collaborate. In addition, China's laissez-faire approach to public health placed it at great risk, as evidenced by the outbreak in 2003 of the Severe Acute Respiratory Syndrome. Since then, major changes to disease reporting, the priority given to CDC including through major new domestic resources and reform of China's health system offer encouragement for CDC. While decentralized funding and varying quality diagnosis, reporting and treatment of infectious diseases remain major challenges, national priority on CDC in China is high.

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There are two things about modern China with which most readers will be familiar. The first is that it is the world's most populous nation: recently released census data revealed that China's population in 2010 approached 1.34 billion. This is below the figure of 1.4 billion anticipated,

as the growth rate of 0.57% per annum has fallen substantially. China's population, along with that in the rest of the world, began to grow very rapidly from the mid-18th century, from an estimated 177 million in 1750 to approximately 430 million in 1850 and 580 million by 1950 (1). The low annual growth rate of only 0.3% during the century to 1950 changed with the relative political stability since 1949; the population sky-rocketed in the 1950s and 1960s. This resulted in public advocacy on family planning ("later, longer, fewer") and finally the one-child policy that has applied to around two-thirds of couples since the late 1970s (2). The need for population control in China was based not only on the formerly high fecundity of Chinese women, but also the rapid fall in the crude death rate that accompanied the establishment of the People's Republic of China (PRC). This fall was largely due to communicable disease control (CDC).

The second familiar aspect is China's meteoric economic development, with an average annual growth rate of around 10% over the last 30 years. China's economic performance is now a major influence on global financial markets, with the developed world now heavily dependent on China's continued growth. Less familiar is the fact that this stellar economic performance only commenced in the second half of the 62 years since 1949.

Both of these familiar aspects of China almost certainly depend heavily on the fact that China's population, for the most part, became relatively healthy compared to residents in nations at a similar stage of development during the first 30 years of the PRC, and certainly much healthier that it was in 1949. By 1980, life expectancy in low-income China (67 years) exceeded that of most nations of similar gross domestic product per capita by seven years (as estimated in 1984), and indeed exceeded that of many middle-income nations (3). Although with some exceptions the health of China's population depends now largely on control of non-communicable diseases (NCDs), the foundation of China's population health, particularly the amazing growth in life expentancy from an estimated 32 years in 1949, depended almost entirely on CDC.

This paper provides an overview of CDC in China since the defeat of China's Nationalists by Mao Zedong's Communists. With regular reference to the contemporary political and economic context, it first describes what is known about disease epidemiology and causes of death before 1949, the strategies used in CDC and the major achievements made in the next 30 years. It follows with a description of the decline of CDC and community-funded public health in the context of China's economic reform, the vertical and vertically-funded disease-control programs and, through SARS, the awakening in China of the risk posed to the people and the nation of ignoring disease surveillance and a population-level approach to public health. The paper finishes with an overview of the status of certain communicable diseases and CDC in China in 2011, and analysis of the impact of China's current health system reforms on this issue.

1949–1979: COMMUNICABLE DISEASE CONTROL AND MORTALITY REDUCTION ON A MASS SCALE

When the Communists founded the PRC in early October, 1949, they established control of one of the most impoverished nations on earth. After a century of domination by Europeans, the fall of the Qing Empire was followed by partial Japanese occupation and a 38 year civil war. The vast majority of the population were engaged in subsistence agriculture, and a survey on the causes of death conducted in 1929–31 revealed that more than half of all deaths were caused by infectious diseases. A list of leading health problems before 1949 (**Table 1**) is noteworthy for the virtual absence of non-communicable diseases (King and Locke, 1983; as cited in ref. 1), and rural health care was in very poor supply (4–6).

Early disease-control programs

The political turmoil and slow socioeconomic development in China between 1949 and 1978 obscure its impressive progress in population health during those years. The Communists were quick to make good on promises of land-reform and establishment of a national "people's" government. In 1950 a Marriage Law was enacted, providing equal rights for women, and the first National Health Congress established a focus on rural health, disease prevention through campaigns, and collaboration between western and traditional Chinese medicine. The focus on improving rural health and on CDC persisted until the 1980s.

Early efforts in public health included work on vaccination, environmental sanitation and hygiene (including the early introduction of composting of night-soil to reduce the concentration of intestinal parasites) and the development of organized CDC programs. Incredibly, between 1950 and 1952, over 512 million of China's ~600 million people were vaccinated against smallpox, massively reducing case numbers; the last outbreak of smallpox in China occurred in 1960, 20 years before global eradication (7). By 1957, more than two-thirds of China's then ~2050 counties had an epidemic prevention station (EPS) or more specialized centres for the control of specific diseases (such as malaria, plague, schistosomiasis, leishmaniasis and brucellosis) modelled on those established in the Soviet Union earlier in the 20th century. Their efforts included "patriotic health campaigns" focusing on ensuring

Table 1 Major health problems in China before 1949*

INFECTIONS			OTHER CONDITIONS
Amoebic dysentery	Japanese B encephalitis	Schistosomiasis	Bronchitis
Ancylostomiasis (hookworm)	Leishmaniasis	Smallpox	Diabetes
Anthrax	Leprosy	Syphilis	Encephalomyelitis
Ascariasis (roundworm)	Leptospirosis	Taeniasis	Fluorosis
Bacillary dysentery	Malaria	Tahyna fever/encephalitis	Kashin-Beck disease
Brucellosis	Measles	Tapeworm	Glaucoma
Cholera	Mumps	Tetanus	Goiter
Clonorchiasis (liver fluke)	Paragonimiasis	Tick-borne relapsing fever	Keshan disease
Dengue fever	Pertussis	Trachoma	Malnutrition
Diphtheria	Plague	Tuberculosis	Nephritis
Enterobiasis (pinworm)	Pneumonia	Typhoid/paratyphoid	Opium addiction
Epidemic meningitis	Polio	Typhus	Rickets
Fasciolopsiasis	Rabies	Varicella	
Filariasis	Rheumatic fever	Viral haemorrhagic fever	
Gonorrhoea	Ringworm	Viral hepatitis	
Influenza	Scarlet fever		

*Data adapted from Banister, 1987 (1).

a clean environment and safe drinking water, vector control, latrine construction and human waste disposal. Each of these short-term interventions (on average twice a year, lasting for around a week) required the mass mobilization of peasants, and so served to increase the "health literacy" of the rural population (1,6–8).

Apart from targeted vaccination, other nascent disease control programs emerged. As a result, cases of typhus dropped by 95% in the 1950s, and there were also major attempts to control gonorrhoea and syphilis (considered by the communists to be social diseases associated with liberal western attitudes and affecting up to 50% of some population groups), first with imported and then domestically produced penicillin. Prostitution was also outlawed and the status of women elevated (6,9–11). Vaccination and campaigns against diphtheria and tuberculosis (TB) also commenced in the 1950s. In the late 1950s, another campaign to "exterminate the four pests" (sparrows, rats, flies and mosquitoes) was avidly implemented, albeit with major negative results when the exploding locust population decimated crop harvests, contributing to famine from 1958–1960 (1,7).

Newborn and puerperal infection rates also decreased tremendously during this period, with the re-training of up to 750 000 traditional midwives and establishment of 2380 maternal and child health (MCH) centres by 1952. No other type of medical facility increased at this rate, and a major result was the decline in neonatal tetanus, down from up to 5% of all newborns to a fraction of this figure (1,6).

Whilst tremendously successful, these mostly preventive care efforts, however, do not infer that rural Chinese had access to clinical care in the 1950s. Patriotic health campaigns were highly effective in CDC but were rarely sustained for more than a month; diseases not addressed by the campaigns were simply neglected and curative care was virtually unavailable outside the cities. Medical schools primarily trained doctors for hospital work. Rural Chinese basically only had access to Chinese herbal medicine and other traditional healers until well into the 1960s (1,6).

In addition, the patriotic health campaigns occurred in the context of major political instability in China. After liberation of the masses in 1949 and a period of relative self-control by peasants of their newly acquired land and produce, Mao introduced a set of disastrous social and economic policies involving community and agricultural collectivization. Motivated by jealousy of the Soviet Union and the west and his perspectives that the rural masses should be both self-sufficient and the source of grain for the cities, Mao promoted the Great Leap Forward from 1958–1960. This included new cultivation methods that failed dismally, further reducing the harvest. Impacted also by adverse weather and the locusts, the resulting famine resulted in the death by starvation of tens of millions, temporarily halting the rapid population growth wrought by successes in CDC.

Village doctors bring curative care, knowledge and a public health approach to the masses

After the disastrous Great Leap period, Mao retreated into the political background and China entered a period of relative political quiet in the early 1960s. Collectivization was relaxed and the patriotic health campaigns continued. EPSs grew in number, reaching around 2500 by 1965 (7), and vertical CDC programs expanded. With a return to food security (albeit with rationing), population growth resumed and life expectancy continued to grow (1). However, unhappy with his perception that the revolution was faltering, development was slowing and that his own political star was fading, in 1966 Mao launched the Cultural Revolution, throwing China into a ten-year period of political and economic chaos. The Revolution was characterized by mass mobilization of urban youth against author-

ity, closure of higher education institutions and a "return to the countryside" policy to pursue revolution as an abstract concept (6).

One positive element of this period, however, was the establishment of a village level cooperative medical scheme (CMS) managed by "barefoot doctors", a new cadre of community-level health worker who brought basic curative care, health education and a continuous rather than campaign-style public health approach to rural peasants (12). Later hailed as the foundation of primary health care (13), China's barefoot doctors rose in number from around one million in 1970 to a peak of around 1.8 million in 1977. Many barefoot doctors were selected from, functioned in the context of and were largely funded by local production brigades (roughly 1000–2000 people in a geographic area) or teams (200–400 people). These brigades had replaced the failed, larger communes established during the Great Leap years, and apart from their commitment to providing grain to the national coffers at fixed prices, were semi-autonomous. Other barefoot doctors were selected from among the urban youths who were "sent down" to the countryside, ill-equipped to farm but educated and literate enough to be trained in basic health care. As a result, and also because each brigade had variable financial capacity to fund its CMS, the quality of health care provided by the barefoot doctors (and an even more basic cadre of community health worker, the health aide, whose numbers added an additional 3.7 million to the community health workforce in 1970) varied widely (**Figure 1**). It also depended on the level and quality of training (which varied from one to six months in duration) and supervision. Some villages also benefited from physicians who had been sent down from the cities for ideological re-education but continued to provide health care, and also from oversight by the EPS team at county level (6,12,14).

The roles of the barefoot doctors and health aides included environmental sanitation, health education, disease screening, surveillance and control, basic clinical care or referral and family planning. CDC continued to benefit from management of water sources and disposal of human excreta (including through composting), improvements in wells, toilets, stables, cooking areas and the local environment, and specific disease control programs through reducing stagnant water, spraying and other measures to control flies, fleas and mosquitoes. Although the barefoot doctors continued the "prevention first" approach to CDC established in the 1950s under the guidance of the Patriotic Health Campaign Coordination Office (a quasi-Ministerial agency only absorbed into the Ministry of Health in 1989), clinical links were established via a three-tier referral network from village through commune to county levels, with supervision in the reverse direction. This three-tier network persists today (7,15,16).

Although politically inseparable from the prevailing harsh limitations on personal expression and movement (6), CDC in China in the late 1960s and throughout the 1970s thus benefited from a large cohort of community-level staff (health aides, barefoot doctors, sent-down physicians and also midwives) with a basic knowledge of health and hygiene (14). These cadres continued the "serve the people" philosophy of the patriotic campaigns initiated in the 1950s, but with a bottom-up rather than top-down approach (4) and, along with other determinants, especially education, contributed in a highly cost-effective way to the continually plummeting crude death and child mortality rates, rising life expectancy and to CDC in rural China.

Perspectives on the origin of China's village doctors. The rationale for the introduction of the barefoot doctors, and their impact, has interested recent scholars, and the different perspectives are summarized in **Figure 2**. One thesis holds that they were part of Mao's goal of improving the level of literacy in China, itself the antithesis of the contemporary philosophy that education was bourgeois (17). In support of this theory is the observation that improvements

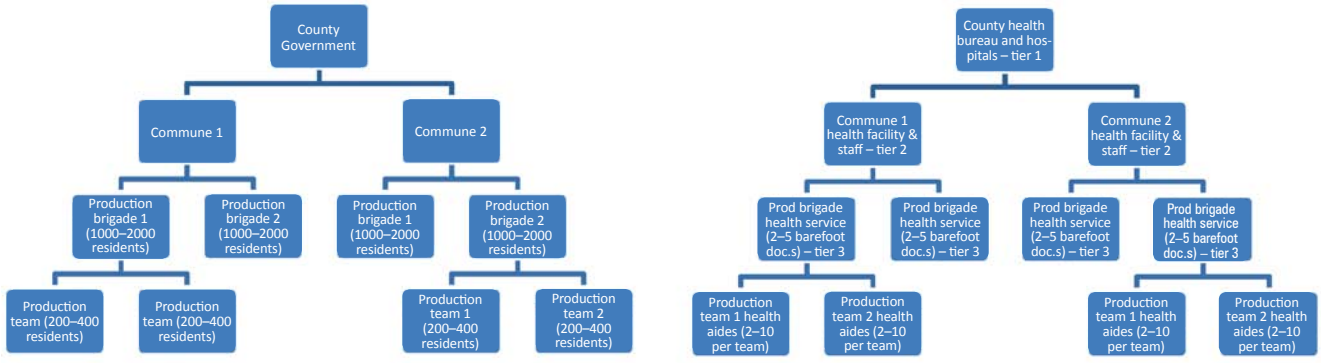

Figure 1 The rural government and health system in 1960s–1970s China, depicting the three-tier network.

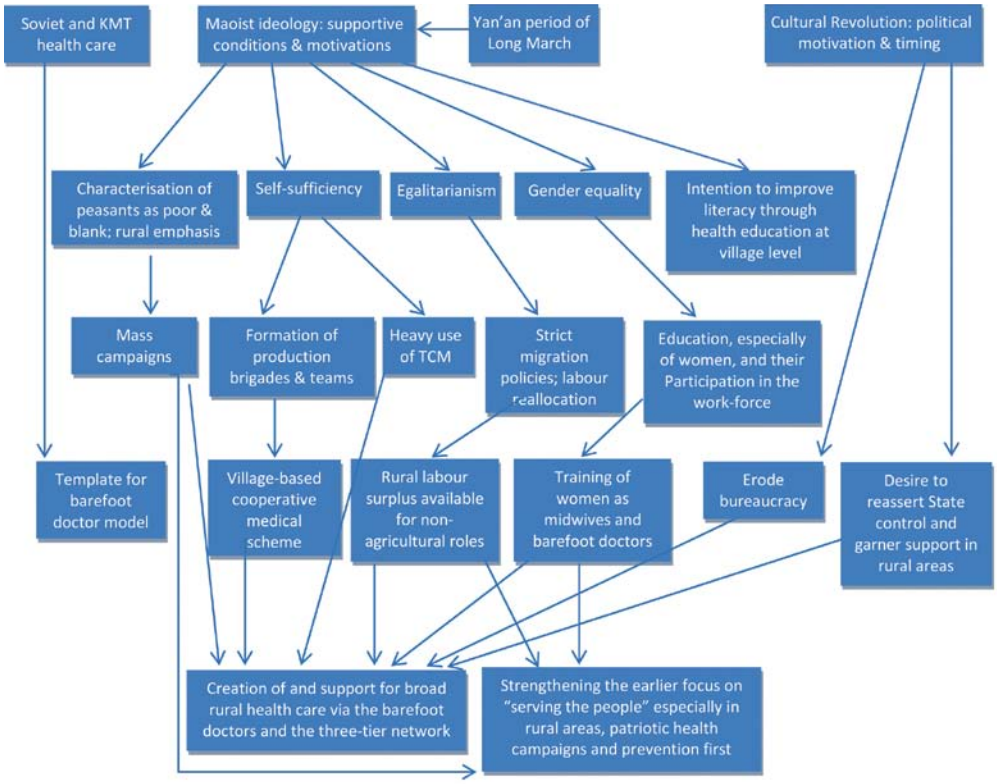

Figure 2 Origins and determinants of China's barefoot doctors program (after Bien, 2008; ref. 6).

in education complemented the public health campaigns in reducing mortality (8). Another points to three influences: (i) models provided by Guomindang experiments on basic primary health care in the 1930s and 1940s, and the Soviet 'feldshers' (field doctors who provided primary health care at village level, supervised by trained staff at higher levels); (ii) the ideology of self-sufficiency, gender equality and egalitarianism (with the peasants as the agents, not just the beneficiaries of revolution), taken up by the Mao and the Communists in Yan'an in the 1940s (also giving rise to the preference for the traditional Chinese medicine practiced by barefoot doctors) and (iii) the political situation in the mid-1960s, which gave rise to Mao's contention that the urban elite (including the Ministry of Health) was ignoring the backbone of the Revolution, the rural peasantry (18), and undermining his reliance on them for his own status. Having failed at commune level during the Great Leap years, self-sufficiency was instead introduced at the more stable village or brigade level, represented in the health sector by the barefoot doctors and the CMS. Whilst benefiting the health status of the population, the benefit for the nation as a whole through collectivization at this lower level was the resulting reliable supply of grain for the cities (6).

Another feature of this period that facilitated the success of the barefoot doctor movement was the surfeit of labour generated by the burgeoning population, movement restrictions that kept the rural population above 80% of the total until 1979 and the relocation of educated urban dwellers to the countryside. Sent-down physicians and urban-educated barefoot doctors made the most of the relative physical ease and prestige of their work, and the fact that income was somewhat less dependent on state-controlled grain prices (6,14).

Finally, the focus on gender equity was another significant influence on the success of the barefoot doctor movement. Although only one third of officially designated barefoot doctors were female, women made up the majority of midwives and health aides, who also functioned as barefoot doctors and contributed to CDC. Ideologies promoting female participation in the rural labour force provided the barefoot doctors program with a significant source of labour, also contributing to effective MCH programs (6).

Along with various social determinants, particularly education and the emancipation of women, the outcome of the PRC's efforts in CDC and community-funded public health during its first 30 years are remarkable indeed, considering its relatively poor economic progress. A 1984 World Bank report suggests China was already entering the epidemiologic transition in the mid-1970s, with deaths due to communicable disease down to only 25%, compared to 44% in other low income countries and virtually all deaths be-

fore 1949 (3). Other reports document an increase in life expectancy from 35 to 68 years, a fall in the crude mortality rate of around 66% and infant mortality from around 250 to 40 deaths per 1000 live births and a decrease in malaria prevalence from 5.5 to 0.3% of the population, between 1949 and 1981 (7,14).

MARKETISATION AND THE BREAKDOWN OF COMMUNITY-FUNDED PRIMARY HEALTH CARE IN THE 1980S

The introduction of market reforms in 1980 heralded the collapse of China's brigade system, the CMS and the funding for the barefoot doctors (19), many of whom abandoned this work in favour of farming (which became more profitable with the abandonment of collective agriculture), or moved to the cities in the context of relaxed movement control) (20). From 1979 to 1984, CMS coverage fell from 80–90% of peasants to 40–45%, and those schemes remaining offered variable and limited coverage (14). By 1986, rural CMS coverage had fallen to 9.5% (15). The number of the newly-named "village doctors" fell to around 1.2 million by 1984, and their supervision and regular retraining also decreased dramatically (14,21), resulting in falling standards despite them handling almost 50% of the nation's clinical work. Having lost their income from the CMS, village doctors have ever since relied on generation of income from fees and the sale of drugs, resulting in abandonment of public health work and major problems with over-prescribing of drugs and inappropriate use of parenteral preparations (20–25), problems that are only now being addressed (26). Payment for health care became the responsibility of the individual; government spending on health as recently as 2008 averaged less than 1% of the national budget (27) and the plummeting affordability of health care resulted in persistently low rates of rural hospital bed occupancy (15,28) and slower declines in infant mortality and the crude death rate (7,29,30). Urban-rural disparities in health funding, facility quality, staff allocations and service uptake rose dramatically, demonstrating burgeoning inequity in China's health sector (15,21,29). Financial decentralization was applied in both the commercial and public sectors, leaving province and county governments to mostly fend for themselves, with minimal support from the national government (14); government funding as a proportion of total health expenditure fell from almost 40% in the early 1980s to below 20% by 1993 and has remained below this figure until 2007 (21,31). It has risen sharply in recent years. Another source has the government's share of total health expenditure falling from 32% to 16% from 1978 to 2002 (32).

Public health in general and CDC in particular suffered badly in this new marketised milieu, as funding for preventive health services declined and the government adopted a laissez-faire attitude to preventive health (19,33). While overall government health resources increased at an annual rate of 6% from 1980 to 1995, the rate of increase for public health services was only 4.8%. The public health share of the health budget declined from 15–18% in the 1970s to 10.6% by 1995. Hospitals were the winners, as the focus on prevention switched to treatment (19). While the falls in county level public health funding were bad, they were worse at commune (now called township) level, with funds covering less than 60% of salaries and nothing else by 1993 (34). Funding of preventive health activities at village level that characterized the barefoot doctor period totally disappeared over the 1980s, and is only now beginning to recover with China's current health system reforms. One reason for this numeric increase but relative decline in public health funding was the increasing number of public health staff and facilities. As with curative services, government successfully reduced the cost but maintained the operation of public health services and CDC by encouraging self-sufficiency through the charging of fees for inspections and vertical programs, and there is good evidence of reduced wastage and improved productivity and efficiency in this regard (34). However, again there were problems with over-servicing of facilities who could afford the fees and ignoring weaker ones with greater problems. In food safety, this was shown by the rising incidence of hepatitis, typhoid and paratyphoid from 1979 to 1988 (19). Public preventive health activities (public goods without direct benefit to consumers) that were not profitable were often neglected or ignored; fees were even charged for vertical disease control programs (such as those against TB and schistosomiasis) despite national targets indicating their priority in the 7th and 8th five-year plans (7), an acknowledgement of the reliance on their implementation by staff whose participation could only be guaranteed with a financial incentive (or who charged fees regardless of services being notionally free). New charges for specific activities such as vaccination, control of schistosomiasis, TB, leprosy and also MCH reduced their uptake and impact. However, rather than cancel vaccination fees, the government introduced an immunization insurance scheme to counter falling coverage (apparently with good effect) (15), and fees for routine vaccination were only officially banned in 2007; the sale of optional vaccines (including several of the new vaccines recommended by WHO) remains a significant source of income for CDCs in China. Decentralisation of social service funding resulted in differential services according to counties' and townships' ability to fund them and the level of prioritization of public health by local authorities. Vertical lines of communication and control of the health system by health authorities also weakened (19). Administration of township health services gradually devolved from county to township governments, and the

township health facilities divided into clinical and preventive sections, with separate funding, revenue and reporting streams (15). Most EPSs reported to local government rather than to higher levels within the health hierarchy, exacerbating the politicization of data and probability of its desensitization. Local government was usually more concerned with economic than social indicators, and disinclined to report bad news like disease outbreaks. They were also disinclined to spend public money on CDC when they could use it to make the county rich.

In this context, the Ministry of Health had a limited role in initiating and sustaining public health programs. The 1989 Law on Control of Infectious Diseases and associated regulations conferred authority and responsibility to act on local governments, the EPSs, specialized institutes and hospitals (7), but these were weakly implemented. Despite encouraging descriptions of a computerized national disease reporting system and surveillance points and associated auditing (35,36) (**Figure 3**), and the piloting of a model CDC centre in Shanghai from 1998 (37), China did not commence modernization of its public health services until 2002 (38), when the old, mainly academic Chinese Academy of Preventive Medicine and county and provincial EPS network was replaced by a revitalized network of Centres for Disease Control modelled on those in the United States and dedicated to public health. There was no compulsory notifiable disease reporting system until 2004. **Figure 3** depicts the disease reporting system that applied from 1985 to 2003, the years of marketisation and the collapse of coordinated CDC. The system was characterized by poor enforcement and weak oversight; annual reports showed that some health providers and hospitals did not bother to report data. During the early weeks of the Severe Acute Respiratory Syndrome (SARS) in 2003, the multiple treating facilities were either not reporting cases, or were reporting to multiple different and non-coordinated authorities (39).

VERTICAL DISEASE CONTROL PROGRAMS REPLACE COMMUNITY APPROACHES TO CDC IN THE 1990S

As indicated, enormous progress was made on CDC in China in the first 30 years of the PRC, so even ignoring the economic reforms it is perhaps not surprising that the approach to CDC changed dramatically after 1980. In the new environment, abstract problems such as those with hygiene and sanitation that caused common, usually non-fatal diseases like diarrhoea and hepatitis now attracted less attention. Indeed, hygiene and sanitation are good examples of public goods whose priority lagged during this period, and China's progress on the safe water and sanitation

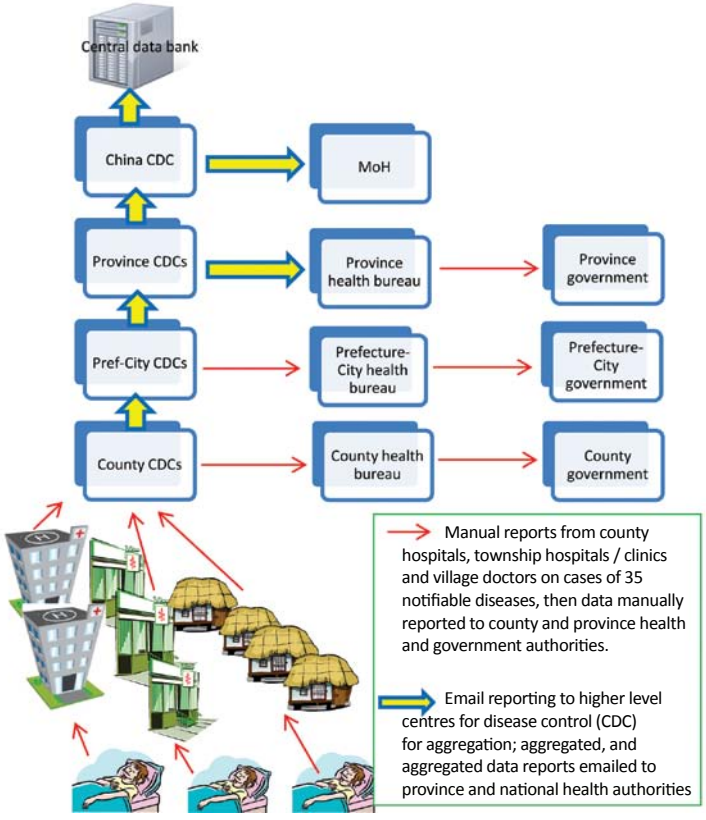

Figure 3 Notifiable disease reporting in China, 1985–2003.

indicators for the seventh Millennium Development Goal has been relatively slow (40).

In this new context, the former campaign approach to CDC was replaced by longer term vertical programs, and several related successes in China are documented even during this period when CDC in China was generally marketised. These include elimination of lymphatic filariasis using diethylcarbamazine-citrate fortified cooking salt (41), marked reductions in malaria and control of poliomyelitis (local transmission of which in China was eliminated from 1996 until 2011) and other vaccine-preventable diseases (7,42,43). For the most part, these successes resulted from disease-specific programs, such as the Expanded Program on Immunisation (EPI) and various other long-term projects. A description of two of these priority disease control programs in the context of CDC in China follows.

Various approaches to the control of schistosomiasis

Schistosomiasis control has been prioritized in China since the 1950s, with various strategies involving coordination between public health, pharmaceutics, agriculture, hydrology, geospatial mapping and animal husbandry experts. The success of this coordination indicates the level of associated political support, but as explained above, this was not always a given. Researchers have also highlighted the impact of farming practices, population movement and China's economic progress on control of this disease (44). In the 1950s, hundreds of millions in 12 southern provinces were at risk of this disease, and around 2% of China's population was infected (45,46). Early control efforts focused on transmission control, especially by early mass mobilization of people to alter snail habitats (45). With the introduction of praziquantel in the early 1980s (47) the focus changed to morbidity control, and mass treatment funded by a World Bank loan and other activities from 1992–2000 (45). In each case the observed reduction in infection numbers was at risk when priority and funding for control programs declined (46). After completion of the World Bank project, case numbers rose again in certain areas (48); the concentration of cases in poor rural areas and the lack of funding for preventive health care in general led to diminished control efforts, leading national health authorities to rate schistosomiasis control, tuberculosis, hepatitis B and HIV as equally critical priorities, in contrast to its status as a neglected tropical disease in other nations (49). Schistosomiasis persists in seven provinces, in a much smaller area of the upper and lower Yangtze River catchment and particularly in villages whose population totals around three million people (41). National funding was required to kick-start new control efforts including periodic mass chemotherapy, reduction of infection sources (animal management, mechanization of farming, water supply and sanitation measures) and public education, supported by a 2004–2015 government-funded vertical project (49–51). Based on infection rates among the population and cattle in the affected areas, this is apparently the most successful combination of activities yet, and the screening program being undertaken has also demonstrated an impact on rates of infection with the soil-transmitted helminths *Ascaris lumbricoides* and *Trichuris trichiuria*, probably as a result of the sanitation and public education components (51).

Tuberculosis – persistently high case numbers despite effective diagnosis and treatment

TB is probably the most important communicable disease that China has struggled to control. China has the world's second highest number of cases of TB (after India) and accounts for 16% of the world's disease burden. It is estimated that around 45% of the population are infected with *Mycobacterium tuberculosis*, with rates of infection and active disease much higher in rural and western areas; cases number around 1.5 million per year, and deaths around 160 000. Again, TB has been the focus of several large externally-funded projects in China over the last two decades, focusing especially on the introduction and expansion of the five-component Directly Observed Treatment (Short-Course) or DOTS strategy promoted by the World Health Organisation. These were effective in treating patients identified and appropriately referred to dedicated TB facilities, but relatively ineffective in improving case-detection and suffered from many of the same problems as the immunization and schistosomiasis programs. Several reports concluded that there were socio-economic barriers to care-seeking, failure or delay in referring patients for available free treatment (due to loss of income by referring clinicians), weak coordination between hospitals and public health authorities and weak local political and financial prioritization of TB case detection and management (that is, weak co-funding), particularly in poorer counties (52,53). The nature of TB as a disease affecting the poor, the itinerant and those least able to pay for treatment applies in China as elsewhere; absolute case numbers have increased with the population and the problem of multi-drug resistance, currently around 8% of cases, is rising.

Overall TB control in China was another example where CDC suffered due to lack of public funding in poor areas, marketisation of the health sector resulting in lack of patient access to free care, and its handling as a vertical rather than integrated clinical-and-public-health program. More recently, in the context of an overall improvement in CDC in China since 2003, massively increased national funding and improved surveillance for disease using the internet have enabled China to meet and maintain global

TB control targets of detecting at least 70% of new sputum-smear positive cases and curing 85% of them (32,54,55). As with schistosomiasis, the increase in national funding for TB control is very encouraging. However, the same challenges continue to apply to TB control as to CDC and public health in China in general: national and local funding for dedicated and trained staff and services, and making related services accessible and affordable to all, including the mobile population, despite the continued focus on profit in most health facilities.

Control of sexually-transmitted diseases – China's newest vertical CDC program

By contrast to the targets of vertical disease-control initiatives, sexually transmitted diseases (STDs) have re-emerged as a major priority in China due to the lack of such a program. China's legendary success in controlling STDs during the 1950s and 1960s was due to a combination of socialization (in which STDs were portrayed not typically as a sign of "bad behaviour" but as a legacy of the old bourgeois and exploitative society, particularly with respect to women); treatment (destigmatising syphilis and gonorrhoea made mass screening and drug treatment relatively easy), and socio-economic approaches (the banning of prostitution, emancipation of women and creation of employment for poor women) (4,6,10,11). This combination was inseparable from the revolutionary milieu of the time, and despite very high rates of infection during the early years of the People's Republic, helped to "eliminate" STDs from China by 1964 (10,56). This situation prevailed until the liberalization of commerce, movement, social customs and secular changes in sexual behaviour allowed the reappearance of STDs in the 1980s (39,56). There were massive increases in STD incidence and an emerging HIV problem in China in the 1990s (57), and the same problems that have led to difficulties in sustaining control of TB and schistosomiasis have plagued STD control: lack of knowledge of disease prevention and treatment, including HIV, among the poor and some echelons of the health sector (58); lack of physical and financial access to good care, along with profiteering by health providers; lack of funding for screening programs, and poor coordination across sectors (including within the health sector, between MCH staff and other clinicians), creating an urgent problem (59,60). According to a former director at China's National Centre for Women's and Children's Health, in 2008: "In the past fifteen years, the prevalence of congenital syphilis increased by 2000 times in China, excluding foetal deaths, stillbirths and abortions caused by syphilis during pregnancy. Surveillance data reveal the incidence of congenital syphilis increased at the rate of 72% each year from 0.01 in 1991 to 35 in 2006 per 100000 live births" (Wang Linhong, former Director, National Centre for Women's and Children's Health at China CDC, personal communication). Syphilis is now numerically the third most common reportable infectious disease in the PRC, behind viral hepatitis and TB (Dr Yang Weizhong, China CDC, personal communication). To its credit, the government has again massively increased funding for education, screening and treatment of STDs, including HIV (60), but the long term success of these measures will again depend on the level of uptake of these activities, fair access to care and local government support.

CHINA'S WAKE-UP CALL ON CDC: IMPROVEMENTS SINCE SARS AND HEALTH SYSTEM REFORM

For both TB and schistosomiasis, it is evident that cessation of internally- and externally-supported disease control programs in the early 2000s was a major setback. Outside the academic and public health community in China, interest to fund and implement programs to control specific diseases associated with poverty and under-development was low at this time. As a result, despite improvements in nutrition, socio-economic status and health infrastructure, there was little progress in infectious disease rates and suggestions that some were increasing slightly during this period (30), although it is likely that this also reflected improved surveillance and diagnosis (39). What was undoubted, however, was the increasing urgency of major reform to CDC and China's health sector in general (29,61–63) due to worsening equity (21, 64–66), a high level of public complaint and government acknowledgement of the problem. Crystallising the situation in the most humbling way came the SARS outbreak in early 2003, which forced China's government and health authorities to act quickly and decisively on the dangerous situation with respect to CDC and, albeit more slowly, on the reform of the health sector.

Much has been written about China's initial denial of the extent of the SARS outbreak (67), and the implications for its control (68). The events occurred despite preceding attempts to renovate the EPSs, as described above, but there is no denying that China remained grossly ill-equipped to deal with a disease of this nature in 2003, and government hugely increased its support for CDC (physical infrastructure, staffing and funding) after this shock (39). Two other major CDC-related impacts of SARS in China were undertaken. First was the revision of the Law on Infectious Diseases in August 2004, mandating the reporting of 37 notifiable conditions, including immediate reporting of certain diagnoses and replacing a system which had essentially become optional and mainly answerable to local government, not the CDC hierarchy. As a result, in restoring its population health objectives CDC was mainstreamed in China's health sector, with both the curative and disease-control

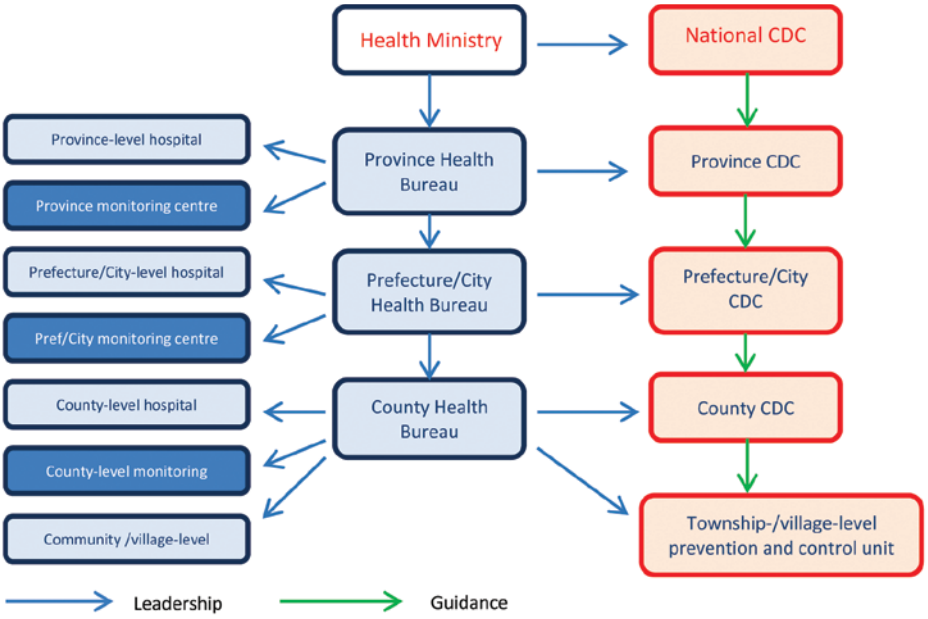

Figure 4 China's new infectious disease prevention and control system, introduced in 2004 (after Yang Weizhong, personal communication, 2010).

sectors responsible for prevention, reporting and management of infectious diseases (Dr Yang Weizhong, China CDC, personal communication) (**Figure 4**).

Second was the development of a new electronic notifiable disease reporting system to answer the central government's request for a case-based, national, integrated and web-based system (incorporating notifiable diseases, risk factors, emergencies and also specific systems for reporting certain diseases like TB, influenza, plague and HIV). In contrast to the old system of weekly and monthly consolidated reports, the new system uses the internet rather than email to upload disease information, not only from local CDC facilities but also from hospitals and health inspection agencies, enabling analysis of data pertaining to reportable diseases and identification of disease outbreaks and trends in real time (**Figure 5**).

Again, the mandating of hospital reporting drew the clinical sector into CDC as never before, raising clinicians' awareness on the public health significance of their actions on infectious diseases and population health; the coverage of this reporting system in 2009 was 100% of CDC-facilities, 97.8% of county-level or higher hospitals and 83.8% of township/village-level facilities, up from 66% in 2007, and the delay in reporting of and entering a notifiable disease report is reported to have dropped from almost 5 and 3.5 days, respectively, to less than one day (Dr Yang Weizhong, China CDC, personal communication). Additional surveillance continues through the notifiable disease reporting system and specific surveillance systems for HIV/AIDS and other STDs, TB, EPI target diseases (for example, for acute flaccid paralysis and measles) and others. The impact of these two initiatives is evident in the rise in the number of notifiable disease reports since 2003 (39) (**Figure 6**).

Alongside these two broad CDC initiatives, a number of disease-specific, donor- and particularly government-funded initiatives have also demonstrated an increased commitment to CDC in China. These include massive increases in funding for control of TB, schistosomiasis, malaria and STDs; treatment and prevention of maternal-to-child-transmission of HIV/AIDS; prevention, screening and treatment of other STDs; vaccine-preventable diseases (such as control of measles through various provincial campaigns and a national campaign in September 2010; control of hepatitis B through catch-up vaccination of older children; expansion of routine immunization to cover 12 antigens since 2007; an enormous program of subsidies to encourage hospital delivery and prevention of neonatal tetanus (also enabling dramatic increases in birth-dosing with hepatitis B vaccine) and introduction of a national child immunisation registration and information system); infectious disease surveillance during emergencies (including use of mobile phones to report on disease incidence in the areas affected by the Sichuan earthquake) and public education campaigns and research to reduce the risk of emerging threats such as recrudescence of dengue fever; increases in brucellosis, zoonoses and the impact of annual outbreaks of influenza and EV71 infection (data available upon request). Both GAVI and the Global Fund for AIDS, TB and Malaria have also supported large scale CDC activities in China in recent years.

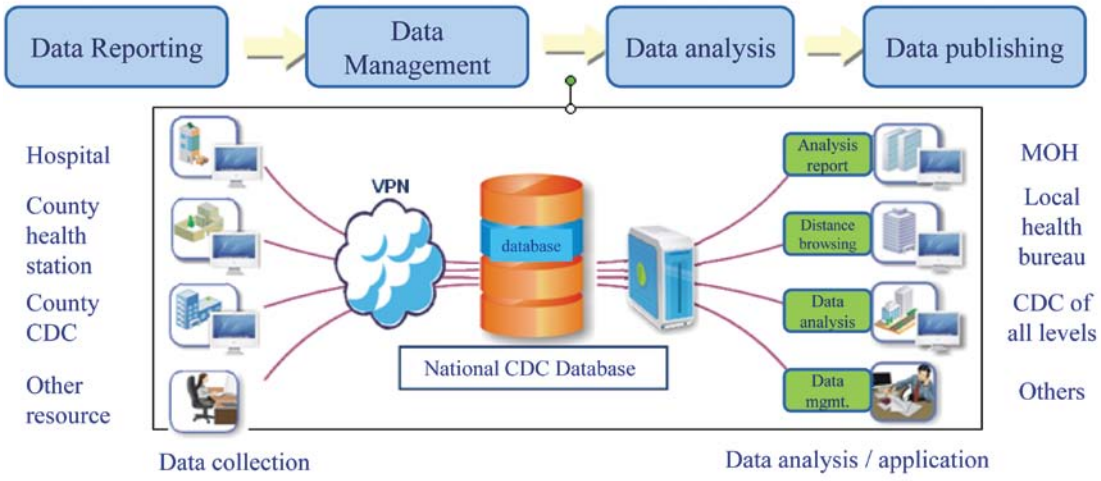

Figure 5 China's web-based notifiable infectious disease direct reporting system (Yang Weizhong, China CDC, permission to reproduce received).

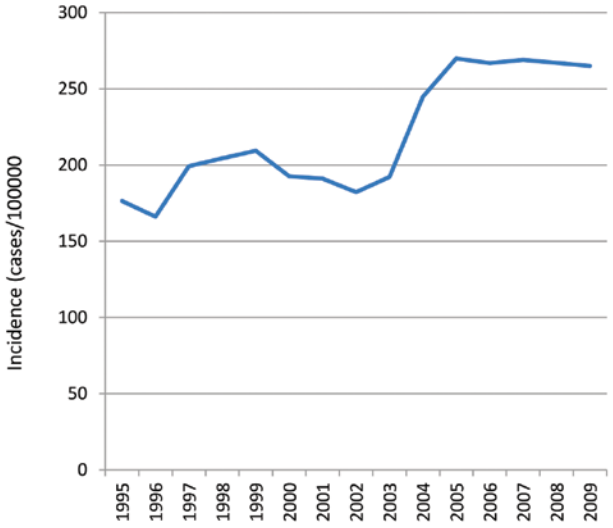

Figure 6 Improved notifiable disease reporting since introduction of real-time system in 2004 (after Wang (39) and data presented at an International Symposium on Research and Control of Infectious Diseases of Poverty, Shanghai, China, 2010).

These developments have since 2009 been taking place in the context of other major developments in China's health sector, some of which are likely to directly benefit CDC. Among the initiatives being rolled out as part of China's health system reform (HSR) are a 15 (now 25) yuan-per-capita public health subsidy for grassroots-level providers, to facilitate their implementation of nine public health activities at village level; including health promotion and implementation of CDC; a National Essential Drugs Scheme intended to control prescribing practices and profiteering by village and township doctors, including in the treatment of infectious diseases (26), and even more funding to improve the staffing and physical infrastructure of China's health system (69).

RISKS AND CHALLENGES

There is no doubt that China is in a much better position to handle another disease outbreak like SARS; indeed, the response to the ongoing highly-pathogenic H5N1 and 2009 H1N1 influenza outbreaks, despite accusations of under-reporting and heavy-handed quarantine of travellers, demonstrate China's increased capacity and intention to act quickly, decisively and in unison across national, provincial and county levels on CDC when population health is threatened.

In fact, the major reasons for slow progress in some aspects of CDC overall is not unique to CDC, nor to China. Decentralisation of the funding and implementation of many health programs in China and elsewhere, although forced upon governments by economic reality and the need to build capacity and encourage the taking of responsibility, is inimical to consistent, reliable and robust outcomes. To the extent that China is relying on poor, predominantly rural provinces and counties for CDC, the wait for elimination of infectious diseases dependent on more than drugs and vaccines may be a long one.

Another problem, also not unique to China but perhaps less tolerable in a nation of its size and importance to global health, is the opacity of the situation at certain times. Despite marked improvements in disease surveillance and CDC since SARS, a remarkably similar and concerning reluctance to report disease outbreaks in times of political sensitivity persists. Recent examples include the likely cover-up of the

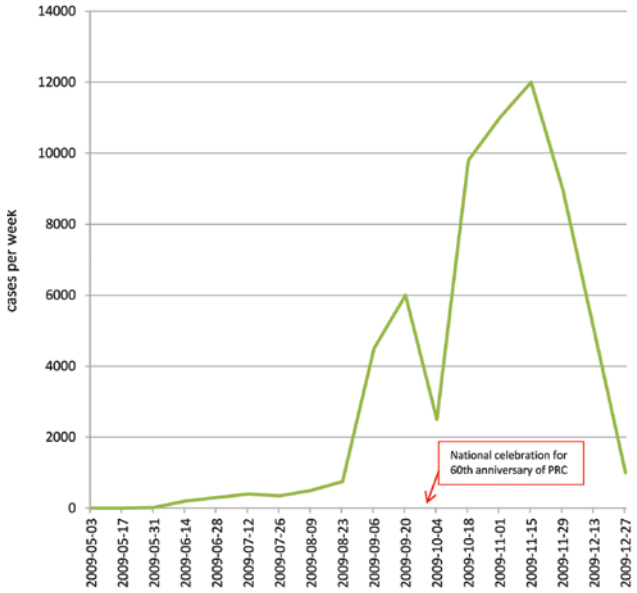

Figure 7 H1N1 case numbers in China by fortnight, May – December 2009 (based on data presented at an International Symposium on Research and Control of Infectious Diseases of Poverty, Shanghai, China, 2010). PRC – People's Republic of China.

melamine scandal before the Olympic Games in 2008 (70), and the probable under-reporting of cases of H1N1 influenza just prior to the celebration of the 60th anniversary of the People's Republic in October 2009 (**Figure 7**). The ongoing tendency of those in power in China to put nationalism and politics ahead of public health at certain key times suggests a continuing risk for CDC (71).

China has not yet taken up global recommendations to vaccinate all children against rotavirus, *Pneumococci, Haemophilus influenza* type b and human papillomavirus. Although the national incidence of rotavirus diarrhoea is almost certainly lower than previously thought (72), a case could easily be made for introduction of the vaccine in poorer provinces or in rural areas, on mortality, morbidity and possibly economic grounds. The same could be said for the two respiratory pathogens, but the data is scant and there has been a long-standing reluctance to introduce these vaccines in China, for two reasons: first, given that China does not use any of the newer combination vaccines it will further complicate an already-crowded vaccination schedule; second and more important, local manufacture of most of these vaccines has not yet commenced, and China does not use imported vaccines in its EPI. These and other so-called category B vaccines are available for private purchase from CDC facilities across China, but there are no data on coverage. It is safe to assume that those who would benefit from them most do not receive them.

Other risks for CDC in China have recently been studied by experts and some are perceived to remain significant. These include the risk of population mobility, persistent proximity of humans and animals in some areas, the regular appearance of new strains of influenza and other pathogens in China, behaviour changes impacting on STDs and the continued low standard of clinical care in poor areas (68,73).

Finally, TB is not the only bacterium for which antibiotic resistance is a major emerging problem in China. Marketisation of the health sector, all the way down to village level, resulted in massive overuse of antibiotics, and a very active pharmaceutical manufacturing sector has avidly promoted "new, improved" drugs to health providers across the nation. Although data are hard to come by as clinical microbiology is a luxury not usually purchased by health services in China, it is safe to assume that multi-resistant bacteria are common in China, and pose a threat to CDC in clinical settings.

CONCLUSION

The study of CDC in China provides a fascinating opportunity to understand the early tribulations and achievements of the People's Republic, during which time the top-down campaign-style approaches adopted from the Soviet Union were replaced by a bottom-up approach led by village doctors, supported by township and county cadres and funded by the CMS. The introduction of a market economy, with the breakdown of these grassroots structures and the reliance on vertical programs has challenged CDC in China. Changes to reporting and the structure and priority of CDC after SARS, along with more recent reforms of the health sector and injection of new funds for disease control programs, allows reasonable expectations of further progress in CDC in the world's largest nation.

Acknowledgements: Dr Yang Weizhong, Deputy Director, China CDC, provided permission for reproduction of a slide used in a presentation given at an International Symposium on Research and Control of Infectious Diseases of Poverty in Shanghai, China, June, 2010, as Figure 5. Various facts from this presentation are also cited as personal communications in this paper. The author is grateful for the support of Drs Guo Sufang and Zhu Xu at UNICEF China in preparation of this paper, and to Drs Grant Miller and others at the University of California, Stanford, for the permission to cite their unpublished work as ref. 8, and Dr Yang Li and others at China CDC and elsewhere for the permission to cite their unpublished work as ref. 26.

Funding: This article was prepared based on work undertaken whilst the author was employed by UNICEF China, with additional support from the Australian Society for Infectious Disease and the University of Edinburgh.

Ethical approval: Not required.

Competing interests: The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: No support from any organization for the submitted work; no financial relationships were declared with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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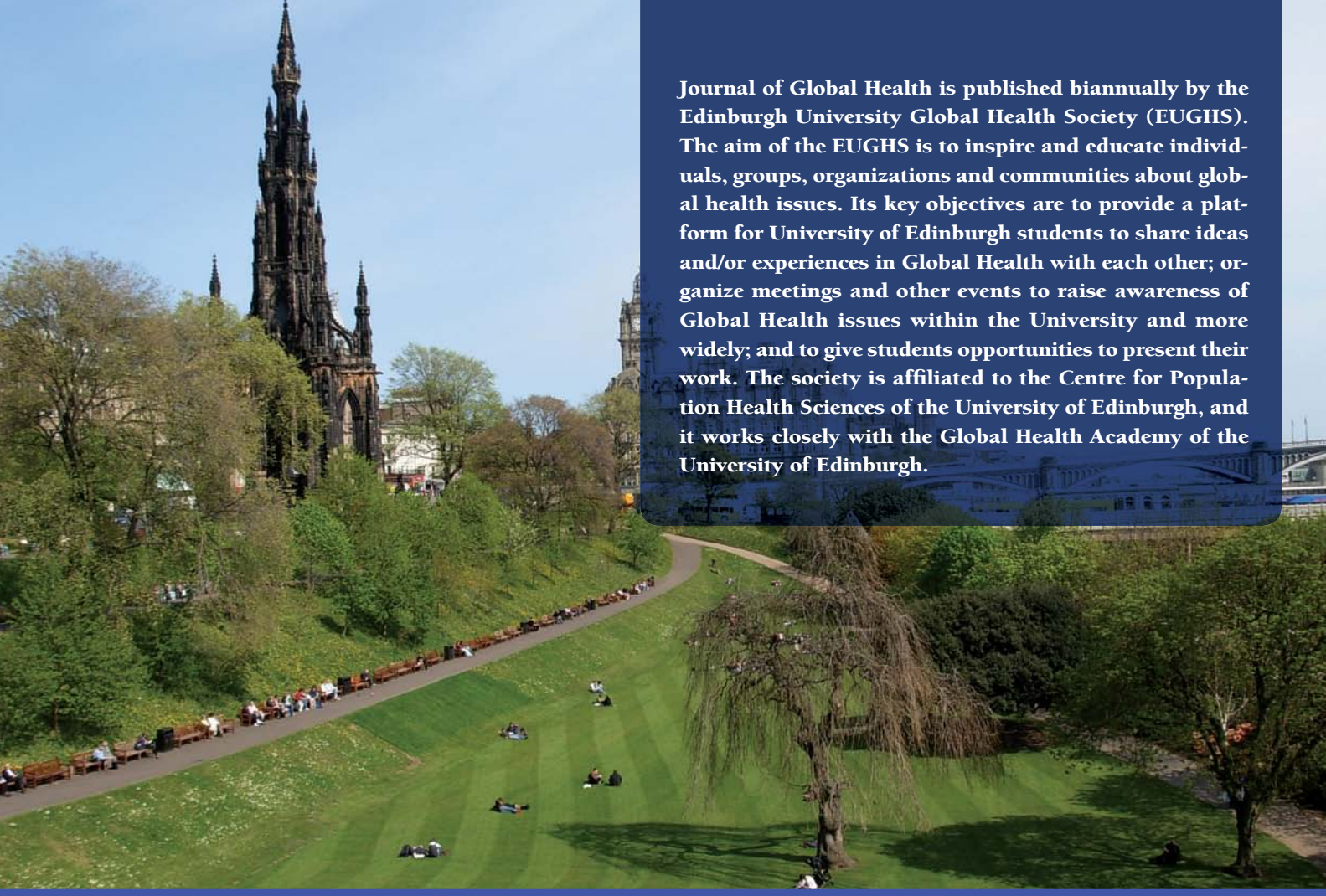

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Subscription (including postage): GBP 30 per any single issue, GBP 50 for annual subscription, GBP 25 for students, GBP 20 for EUGHS members. Please contact JGH office (stephanie.scott@ed.ac.uk) for details.

Journal design: Snježana Engelman Džafić for LASER*plus*, Zagreb, Croatia

Realisation: LASER*plus*, Zagreb, Croatia, www.laser-plus.hr

Printed on acid-free paper.

Journal of Global Health (print) ISSN 2047-2978
Journal of Global Health (online) ISSN 2047-2986

ISSN 2047-2978