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Journal of Global Health (JoGH) is a peer-reviewed general medical journal focusing on issues relevant for global health. The mission of the journal is to serve the community of researchers, funding agencies, international organizations, policy-makers and other stakeholders by providing an independent critical assessment of the key issues that dominated the global health community. JoGH publishes original articles, viewpoints, research protocols and other publication items, making them available in full text online as soon as they are ready for publication.

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A Nepali woman soaks her feet before the debriding of her ulcers at a wound clinic in Lalgadh Leprosy Services Centre in Nepal. Multidrug therapy cures leprosy, stops transmission and prevents disabilities when delivered in timely fashion. Disease stigma and poor treatment access make Nepal one of only a few nations yet to achieve disease elimination according to the WHO definition.

Photograph taken by Ewan D. Kennedy, an Edinburgh medical student working at Lalgadh Leprosy Services Centre, summer 2011.

Journal of Global Health: The Mission Statement

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

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

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

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

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

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

March 7, 2011

The Editors, Journal of Global Health

The first three years of the Journal of Global Health: Assessing the impact

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The Journal of Global Health (JoGH) is three years old. To assess its impact, we analysed online access to JoGH's articles using PubMed Central and Google Analytics tools. Moreover, we tracked citations that JoGH received in 2013 using ISI Web of KnowledgeSM and Google Scholar[®] tools. The 66 items (articles, viewpoints and editorials) published between June 2011 and December 2013 were accessed more than 50 000 times during 2013, from more than 160 countries of the world. Seven among the 13 most accessed papers were focused on global, regional and national epidemiological estimates of important infectious diseases. JoGH articles published in 2011 and 2012 received 77 citations in Journal Citation Reports[®] (JCR)–indexed journals in 2013 to 24 original research articles, setting our first, unofficial impact factor at 3.208. In addition, JoGH received 11 citations during 2013 to its 12 original research papers published during 2013, resulting in an immediacy index of 0.917. The number of external, non–commissioned submissions that we consider to be of high quality is continuously increasing, leading to current JoGH's rejection rate of about 80%. The current citation analysis raises favourable expectations for the JoGH's overall impact on the global health community in future years.

n March 7, 2014, the *Journal of Global Health* (JoGH) was exactly three years old. We published the first three volumes, delivering all on time – both electronically and in print, while adhering closely to our initial concept of the journal content: an editorial followed by a comprehensive summary of global health news, four viewpoints and six articles. We have every reason to celebrate our journal's third birthday, because this is perhaps the most significant milestone in the life of a new journal: the first opportunity when its impact on the wider scientific community can be adequately assessed.

In the not—so—recent—past, when manuscripts were still being submitted in heavy paper envelopes by regular mail, typed double—spaced and photocopied in triplicate, with figures often drawn by hand, and with travel times across the Atlantic of three weeks in each direction, the only way to evaluate the impact of a start—up journal was through the subscriptions and citations that it would attract. Subscriptions to printed copies were almost a necessity, providing funds needed to ensure journal's sustainability, which is why most journals arose from professional societies. The search for citations was done by painstaking browsing through heavy, voluminous books that resembled phone directories of large cities – month by month, author by author, article by article. That was the reality of scientific publishing and impact assessment that had remained fairly unchanged throughout most of the 20th century.

The three JoGH's Editors—in—Chief still remember those times very well, both as authors of manuscripts and as journal editors. However, we are also aware that researchers who started their careers in the 21st century probably cannot even begin to comprehend those times. Article mailing charges could have cost researchers from low—income countries their week's salary, which they were willing to pay despite an uncertain outcome. This obstacle is now replaced in most journals with a faceless electronic submission and electronically generated e—mail replies. The model of financing through subscriptions has been largely replaced, too. Many journals charge access to research articles that they publish. The traditional, reader–pays publishing model is today challenged by the open–access movement. New open–access journals are being launched on an almost daily basis, offering free access to their content, but charging authors for the article processing and publishing costs. Cyberspace has entirely replaced print, and it is difficult for us to remember holding a printed issue of any journal in our hands and reading it, article–by–article, as it was done only a decade ago. Nowadays, PDF versions of individual articles are downloaded, searched using browsers, and stored somewhere in the computer for further reading.

In this sea of change that has completely transformed scientific publishing, there is still one surviving feature that seems fitter than ever: the almighty "impact factor". Although much criticized, terribly flawed in so many ways, calculated in a non-transparent way, generated by a single, now private, enterprise, with numerator and denominator often not containing comparable items, and having a long history of being manipulated to a greater or lesser extent – it still remains the single most effective advertisement for any scientific journal, dwarfing all others by a large margin [1–3]. Therefore, anyone serious about their scientific publishing effort – and we certainly aim to be – simply cannot afford to ignore it, no matter what we may think of it personally.

The impact factor (IF) was instantly and firmly accepted by the scientific community because is successfully reduced all information about a journal's content to a single number. For the vast majority of journals, their IF ranges between 0 and 10: among 8471 journals included in the Journal Citation Reports® Science Edition in 2012, which are themselves considered to represent a selection of the world's journals of the highest quality, 8312 (98.1%) had IF smaller than 10 [4]. This means that only a small minority of the most competitive journals have the IF greater than 10. The IF tells any interested researcher the average number of citations that the articles published by the journal over the previous two calendar years received in the current calendar year. Subsequently, this implies that any articles that attracted 10 or more citations in any calendar year generated a substantial interest in the research community.

There have been developments in recent years that promise to at least provide some validation for the calculated impact factors, if not actually offering a viable alternative. First, the ISI Web of KnowledgeSM Journal Citation Reports[®] (JCR) by Thomson Reuters publishing corporation provides impact factors based both on 2–year and 5–year content follow–up, which prevents and exposes manipulation of the original 2–year metric [4]. Moreover, they also provide the Eigenfactor[®] score and Article Influence[®] score. The Eigenfactor[®] score calculation is based on the number of times that the articles from the journal, that were published in the previous five years, have been cited in the current year, but it also takes into account the quality of the journals that have contributed these citations (ie, citation in a journal with a higher impact factor will influence this score more than one in a journal with a lower impact factor) and it removes a journal's self–citations [4]. The Article Influence[®] score determines the average influence of a journal's articles over the first five years after publication. It is calculated by dividing a journal's Eigenfactor[®] score by the number of articles in the journal, normalized as a fraction of all articles in all publications. The mean Article Influence[®] score is 1.00, and a score greater than 1.00 indicates that each article in the journal has above–average influence, and vice versa [4]. These additional metrics contribute additional validation to the original impact factor alone.

However, this still doesn't address the concern that all measurement of quality of scientific journals seems to be in hands of a single, private enterprise, and is dependent on their choice of the journals that are being followed and that contribute citations. They also make decisions on how to classify journal's published items, which determines the denominator of the IF equation. However, things have changed in this area, too, and competition has emerged. The ISI Web of KnowledgeSM searching tool – Web of ScienceTM [5] – is no longer the only prominent web-based provider of citations to the published articles. Another publishing giant, the Reed Elsevier corporation, have developed their own citation database – Scopus[®] [6]. It is a very similar search tool, although possibly more comprehensive in some areas of science - it covers more than 20000 titles from over 5000 publishers, offering about 20% more coverage than Web of ScienceTM [7]. Both of these search engines require relatively expensive subscription for access. However, Google, Inc. corporation, which states that their mission is "...to organise the world's information and make it universally accessible and useful", have launched their own, free search engine that also tracks citations - Google Scholar[®] [8]. The coverage of journals and academic sources in Google Scholar is not only completely free to the general public, but also much more comprehensive than either Web of Science® or Scopus®. This is because it takes into account citations found in virtually any document that has ever been exposed to the internet, in any shape or form. Therefore, citations to published articles can nowadays be tracked using at least three tools - Web of Science[®], Scopus® and Google Scholar®. They will quote different number of citations, with the first two being less inclusive, and the third one being more inclusive.

In addition to improved tracking of article citations and journal's impact, another metrics of scientific impact has emerged – Hirsch index (or h–index) [9]. Designed initially to capture the productivity of any individual scientists in a single number, this metric can also be applied to scientific journals. *h*-index measures the number of articles associated with a scientist, or a journal -h - that have been cited h times or more. That means that a scientist, or a journal, with h-index of 50 would have published 50 articles that have each been cited 50 times or more. All other articles associated with this scientist would have been cited less than 50 times, and therefore they would not contribute to the score. The beautiful simplicity of this metric and its ability to capture both the quality and the quantity of research output in a single number has made it extremely popular in recent years [10]. Web of Science[®], Scopus[®] and Google Scholar® also provide it in association to research output of individual scientists. Interestingly, Google Scholar recognised its value in evaluating scientific journals, too, and it provides ranking of world's leading 100 journals in different languages by their 5-year h-index, ie, the h-index based on citations to all papers published in the previous 5 years [9]. While impact factor favours journals that publish small, selected number of papers which attract high number of citations each year (such as journals that specialize in publishing review articles), 5-year h-index does more justice to journals that publish large number of quality papers. With h-index, the quantity of published papers becomes a potential strength, as more papers could contribute to h-index; while with impact factor publishing many papers could be seen as a burden to achieving high metric, because they increase the denominator.

Finally, the widespread use of the internet and social media, and the possibility to document and store the information about its usage, has lead to an entirely new way of evaluating the impact of scientific publishing. Given that the papers are now accessed on the Internet rather than by reading printed journals, this allowed evaluation of the impact not only through article, but also through their access and usage. Thanks to tools such as PubMed Central® [11] and Google Analytics® [12], it is possible to follow access and downloads of individual articles in their electronic or PDF forms, tracing them to geographic location and other characteristics of the user. This has shown that many articles, especially those related to policy, are used, read and commented lot more than they are cited. Social media such as Facebook [13] and Twitter [14] allow following of how much immediate impact do research articles generate, and how quickly do their ideas spread through social media - ie, how often are they "shared", "tweeted" and "liked". This allowed a broad, multi-dimensional evaluation of research impact that could not even have been imagined only a decade ago.

So, finally to the point – how did the *Journal of Global Health* do over the past three years, taking into account all those different measures of scientific impact that exist today? We decided to focus on two measures of usage and two citation–tracking tools. The measures of usage are based on online access to the articles through PubMed Central [11] and

through our own journal's website, monitored using Google Analytics tools [12]. The two citation–tracking tools were ISI Web of KnowledgeSM [5] and Google Scholar[®] [8].

Table 1 shows the ranking (according to total access, ie, usage) of the 20 most accessed papers published in the first 3 volumes – between June 2011 and December 2013. The 66 items (articles, viewpoints and editorials) published during this period were accessed more than 50 000 times and from more than 160 countries of the world. Table 1 shows that among all recorded episodes of access, full–text access was typically 2–4 times more common than PDF download. Also, the access occurred about 8 times more frequently through PubMed Central than through our own website, as a result of PubMed searches that pointed to our content.

Seven among the 13 most accessed papers were focused on global, regional and national epidemiological estimates of important infectious diseases: childhood pneumonia (ranked 1st), typhoid and paratyphoid fever (2nd), sepsis (4th), neonatal sepsis (8th), maternal parasitic infections (9th), childhood diarrhoea (12th) and maternal bacterial and viral infections (13th). The high position of those articles could have been somewhat expected, but the most pleasant surprises on the list were the articles on the floods in Southeast Asia as a health priority (3rd), biomarkers for neonatal sepsis (5th), a historical perspective on communicable disease control in China (6th) and malnutrition as a contributor to "double burden of disease" in poor countries (7th). Two further related clusters worth mentioning were three papers on the topic of non-communicable diseases in low- and middle-income countries (ranked 15th, 16th and 20th), and the two research priority-setting exercises that used the CHNRI method (ranked 10th and 18th).

Table 1 also shows that access indicators correspond reasonably well to the number of citations received, especially when analyzed across all 66 published items and normalized for the number of months since the time of the publication. The number of citations recorded by Google Scholar® was typically between 25% and 75% larger than the number recorded by ISI Web of KnowledgeSM. The two most accessed papers also stand out in terms of the number of citations received (especially when this is adjusted for the duration of citing period), but several other papers are already showing that they will likely accumulate at least 10 citations in ISI Web of KnowledgeSM during 2014.

Using the citation data from Google Scholar, we calculated JoGH's impact factor: we added the number of all citations received during 2013 from the journals that are indexed by the ISI Web of KnowledgeSM, and then divided the sum by the number of our "citeable" items published in 2011 and 2012, ie, original research articles published in JoGH (because our viewpoints are published as opinion pieces). JoGH articles from 2011 and 2012 received 77 citations in 2013

Table 1. Ranking the 20 most accessed papers published by the Journal of Global Health in the first 3 volumes (between June 2011 and December 2013).

Rank	Author	AUTHOR TITLE CITATION		Total requests		PDF requests	CITATIONS (WoK)	Citations (Google Scholar)
1	Igor Rudan et al; CHERG group	Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries	J Glob Health 2013; 3(1):010401	3718	2387	1331	5	9
2	Geoffrey C. Buckle et al.	Typhoid fever and paratyphoid fever: System- atic review to estimate global morbidity and mortality for 2010	J Glob Health. 2012; 2(1):010401	2350	1763	587	13	20
3	Jacqueline Torti	Floods in Southeast Asia: A health priority	J Glob Health. 2012; 2(2):020304	2082	1964	118	1	1
4	Issrah Jawad et al.	Assessing available information on the bur- den of sepsis: global estimates of incidence, prevalence and mortality	J Glob Health. 2012; 2(1):010404	1814	1298	516	4	10
5	Mahbuba Meem et al.	Biomarkers for diagnosis of neonatal infec- tions: A systematic analysis of their potential as a point–of–care diagnostics	J Glob Health. 2011; 1(2):201–209	1798	1098	700	4	6
6	David Hipgrave	Communicable disease control in China: From Mao to now	J Glob Health. 2011; 1(2):224–238	1424	1179	245	7	10
7	Ivana Kolčić	Double burden of malnutrition: A silent driv- er of double burden of disease in low and middleincome countries	J Glob Health. 2012; 2(2):020303	1243	999	244	2	4
8	Donald Waters et al.	Aetiology of community-acquired neonatal sepsis in low and middle income countries	J Glob Health. 2011; 1(2):154–170	1171	850	321	2	4
9	Tom K. Roberts et al.	Epidemiology and aetiology of maternal par- asitic infections in low- and middle-income countries	J Glob Health. 2011; 1(2):189–200	1149	764	385	3	7
10	Rajiv Bahl et al.	Setting research priorities to reduce global mortality from preterm birth and low birth weight by 2015	J Glob Health. 2012; 2(1):010403	1128	745	383	5	8
11	Ruth M. Campbell et al.	The importance of a common global health definition: How Canada's definition influences its strategic direction in global health	J Glob Health. 2012; 2(1):010301	1080	899	181	2	3
12	Shelby E. Wilson et al.	Scaling up access to oral rehydration solution for diarrhea: Learning from historical experi- ence in low and high-performing countries	J Glob Health. 2013; 3(1):010404	1006	808	198	1	4
13	Prasad Palani Velu et al.	Epidemiology and aetiology of maternal bac- terial and viral infections in low- and mid- dle-income countries	J Glob Health. 2011; 1(2):171–188	988	761	227	2	3
14	Harish Nair and Rajmohan Panda	Quality of maternal health care in India: Has the National Rural Health Mission made a dif- ference?	J Glob Health. 2011; 1(1):79–86	952	818	134	2	2
15	Anthony Maher and Devi Sridhar	Political priority in the global fight against non-communicable diseases	J Glob Health. 2012; 2(2):020403	911	610	301	5	7
16	Rhiannon George–Carey et al.	An estimate of the prevalence of dementia in Africa: A systematic analysis	J Glob Health. 2012; 2(2):020401	907	611	296	2	3
17	Xing Lin Feng et al.	Social, economic, political and health system and program determinants of child mortality reduction in China between 1990 and 2006: A systematic analysis	J Glob Health. 2012; 2(1):010405	723	520	203	6	9
18	Igor Rudan et al.	Setting priorities for development of emerg- ing interventions against childhood pneumo- nia, meningitis and influenza.	J Glob Health. 2012;2(1):010304	713	417	296	5	10
19	Thor A. Wagner et al.	Emerging biomarkers for the diagnosis of se- vere neonatal infections applicable to low re- source settings	J Glob Health. 2011; 1(2):210–223	709	532	177	3	4
20	Alice Graham et al.	Estimating the incidence of colorectal cancer in Sub–Saharan Africa: A systematic analysis	J Glob Health. 2012; 2(2):020404	709	491	218	3	4

WoK – Web of Knowledge

to 24 original research articles in 2011 and 2012, setting our first, unofficial impact factor at 3.208. In addition, we received 11 citations during 2013 to our 12 original research papers published during 2013, leading to our first immediacy index of 0.917. Our journal's self–citations did not contribute to this calculation because JoGH is still not indexed among the journals that the ISI Web of KnowledgeSM and the Journal Citation Reports® use for computing impact factors [15].

Can we be satisfied with our impact to date? The numbers above are certainly encouraging. When we launched the

journal in 2011, we defined our mission as serving "the community of researchers, funding agencies, international organizations, policy-makers and other stakeholders in the field of international health by 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; providing objective reviews of global health and development issues; and allowing independent authors and stakeholders to voice their personal opinions on issues in global health". We seem to have addressed all those goals to a substantial extent – through publishing a selec-

tion of topical research articles, viewpoints and news items that have been noticed in the global health community. Given that we first appeared on PubMed Central in January 2013, and that the large majority of access to our content is achieved through PubMed searches that return our papers as a result, the total access to our content (more than 50000 requests) has essentially been achieved over a period of a single year. Moreover, this means that our average published paper has been seen nearly 1000 times over the past year - ie, between 2-3 times each day. In addition, we were pleasantly surprised by the fact that we recorded access to our content from nearly every country in the world over the period of just over a year. This is certainly not a negligible impact. Moreover, the current citation analysis raises favourable expectations for the future years, especially taking into account the average time between access to articles and their citations - suggesting that the potential for translation of a considerable recorded access to our published content into citations is yet to be revealed.

The encouraging signs that our journal is taken increasingly seriously among the major players in global health are reflected in the fact that the number of external, non-commissioned submissions that we consider to be of high quality is continuously increasing: while we only received one external, non-commissioned submission in our first year (June–December 2011), we received 6 external submissions in 2012, then 42 in 2013, while the projection for the 2014 based on the first three months is already above 70. We publish a total of 20 items each year, which means that our rejection rate (when all the commissioned papers are added) is already approaching 80%. Another sign of our increasingly notable presence in the global health research community is reflected in the fact that we already have theme issues produced in collaboration with leading global health organizations - Program for Appropriate Technology in Health (PATH) and The Gates Foundation (2013 June theme issue on childhood diarrhoea), Imperial College London's Global eHealth Unit (2013 December theme issue on mHealth), and United Nation's Children Fund (UNICEF - 2014 December theme issue on integrated community case management), at the same time keeping a rigorous peer review process. We are looking forward to further similar collaborations, as a growing evidence of our journal's increasing impact in global health research community.

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Africa

>> In a recent interview, Mr Andris Piebalgs, a member of the UN high-level panel advising on the post-2015 agenda, gave his thoughts on tackling the global crisis of youth unemployment. He highlighted the link between work opportunities and social disruption, saying that the main group of concern is young people in sub–Saharan Africa, with increased expectations and decreased opportunities. In the developed world, the youth unemployed have social protection - lacked by those in developing countries. However, he believes in similar solutions: good primary education; more liberalised and competitive economies; increased trade; and strengthened private sectors. He believes that health, nutrition and the agricultural sector are key to tackling youth unemployment in developing countries, and civil society programmes are important catalysts for getting young people into employment. (The Guardian, 14 Nov 2013)

▶ Nelson Mandela's life, spanning 1918–2013, was defined by courage and a commitment to inclusiveness and equality. His associations with global health are broad and deep, including chairing the Board of the Vaccine Fund, which mobilized resources for the Global Alliance for Vaccines and Immunization. However, his contribution to the battle against AIDS is his greatest global health legacy; he viewed it as the urgent struggle for a new generation, which disproportionately affected the poor in Africa. His fundraising for HIV/AIDS and advocacy work to promote health care and reduce stigma means that his loss is felt particularly strongly in this group. He made human rights central to global political discourse, and moves towards universal health coverage and sustainable development goals owe much to his vision and insight. (*The Lancet*, 9 Dec 2013)

► The first mass vaccination campaign in Africa with a vaccine that does not need constant refrigeration provided complete coverage, and the vaccine stayed viable in temperatures up to 39°C. The meningitis A campaign in Benin is a breakthrough for both the vaccine (MenAfrVac®) and for increasing the efficiency, coverage and affordability of

other vaccines, especially in remote areas where it is difficult to keep vaccines cold. It could reduce the number of under–vaccinated children and the cost of vaccine administration. The vaccine was developed through the PATH– WHO Meningitis Vaccine Project using a development model to provide an effective, affordable and long–term solution to epidemic meningitis in parts of Africa, which has killed or disabled thousands of people over the years. *(PATH,* 19 Feb 2014)

Malawi has one of the highest rates of maternal mortality in the world, and Chief Kwataine, headman of the district of Ntcheu, attributes the root of the problem to a culture of secrecy where sex, pregnancy and childbirth are taboo subjects. This meant that pregnant women were not talking to doctors and nurses, and not accessing the care they needed. He came up with the idea of 'secret mothers' – female elders, respected in their communities – who could break through this barrier to support and advise pregnant women in their communities. The programme seems to have saved lives in the district, and Chief Kwataine is trying to spread it to other villages. (*Public International Radio*, 23 Feb 2014)

>> The first Ebola outbreak in Guinea, West Africa, has killed at least 59 people and may be spreading to other countries. Guinea's Health Ministry said that most of the known cases were in border areas near Sierra Leone and Liberia. The outbreak is of the Zaire strain, which has a 90% mortality rate and there is no known cure. Bats are the virus' natural reservoir, and once humans are infected it readily spreads via bodily fluids. Outbreaks are contained by isolating the ill, and making sure that those treating them wear suitable protective clothing. Education is also crucial to prevent people panicking and fleeing, thus further spreading the outbreak. Médecins Sans Frontières and WHO are working with the Health Ministry to contain the outbreak: the countries threatened by the disease are amongst the world's poorest and cannot mount large public health efforts by themselves. (New York Times, 24 Mar 2014)

Asia

▶ In 2011, developing countries lost nearly US\$ 1 trillion to fraud and corruption, more than received in foreign aid – and it is growing, warns Global Financial Integrity (GFI), a group that exposes financial corruption. The Middle East and North Africa saw the largest increases in the proceeds from illicit business, crime and corruption, followed by sub–Saharan Africa. Asia lost the largest amount of money, but when outflows are measured as a percentage of annual growth, sub–Saharan Africa has the biggest problem, with Nigeria and South Africa topping the list of affected countries. The GFI warns that these illicit outflows have a devastating effect on African economic development and stability. The G20 group of the world's leading economies is addressing this by automatically exchanging tax information to capture tax dodgers and block the transfer of illegal money. (*Thomson Reuters Foundation*, 12 Dec 2013)

▶ The UN appealed for a record US\$ 6.5 billion for Syria and its neighbours, to help the 16 million victims of the 33-month conflict. The appeal covers food, drinking water, shelter, education, health and polio vaccines. More than 100 000 people have been killed, millions displaced, cities have been destroyed and the economy wrecked. Destruction of the water network leaves 10 million people relying on the UN to chlorinate water, and energy supplies are severely disrupted. The UN was cautious about a peace break-through, and stated that even if the violence stops immediately there will be an ongoing need for humanitarian assistance. (*Reuters*, 16 Dec 2013)

▶ Dr Anita Zaidi, a paediatrician from Pakistan, beat 550 entries to win the first US\$ 1 million Caplow Children's Prize. She will use the prize money to help residents of Karachi's Rehri Goth district, whose residents are so poor and isolated from medical services than 11% of children die before the age of 5. She will train midwives and set up transportation networks to take mothers in birth crises to hospital. She will address local prejudices against hospitals, and distribute food, vitamins and vaccines. The prize was endowed by Ted Caplow, an entrepreneur whose premature triplets spent a month in intensive care. (*New York Times*, 30 Dec 2013) ▶ Extreme poverty and a harsh climate means that onethird of Afghan people have insufficient food to lead active, healthy lives, and another third risk food insecurity. Food shortages are particularly damaging to children; more than 50% of Afghan children suffer cognitive and physical damage due to malnourishment in the first two years of life. A UN study found that even a minimally health diet is beyond the reach of the majority of Afghans. To help tackle this, the government has begun fortifying certain foodstuffs with micronutrients. Adequately–fed children can earn between 33–50% more as adults compared to their malnourished peers, and malnutrition reduces Afghanistan's national income by 2–3% annually – a loss of US\$ 500 million to an impoverished country. (*The Guardian*, 26 Jan 2014)

▶ On his first visit to Myanmar, the World Bank's President Jim Yong Kim announced a US\$ 2 billion development program for the country. It will include projects to improve access to energy and health care for poor people, and support other key development priorities. As over 70% of Myanmar's people lack access to reliable electricity supplies, US\$ 1 billion is earmarked to expand electricity generation. Another US\$ 200 million is set aside to help achieve universal health coverage by 2030. An estimated 75% of Myanmar's mostly rural population lacks access to quality health care, and high costs place most essential services out of the reach of many families below the poverty line. (*World Bank*, 26 Jan 2014)

Australia and Western Pacific

▶ Former Australian Prime Minister, Kevin Rudd, has denied any ambitions to lead the UN as Ban Ki–moon's successor. Stating that he always intended to remain involved in global politics, he would not comment on domestic issues. In a speech to The International Institute for Strategic Studies in London, he outlined the repositioning of global power towards China, describing its rise and the impact of international order as "the great challenge of our time." (*The Guardian*, 17 Dec 2013)

Dengue virus serotype 3 recently re-emerged in several countries and territories in the South Pacific, including Fiji, French Polynesia and Kiribati, after nearly 20 years' absence. There are four strains of the dengue virus, and infection with one strain will provide immunity against it but not the others. Dengue serotypes can re-emerge after absences of 15–20 years as children who are growing up without exposure to it create a susceptible cohort. Dengue is transmitted by mosquito bite, and there is no vaccine or

specific treatments. Mortality rates are low provided that it is recognised early and appropriate care is sought. Affected areas are taking action by surveillance, controlling mosquito numbers and clinical care. (*WHO*, 16 Jan 2014)

▶ Australia's federal government will cut Australia's contribution to tackling climate change, health and sanitation crises in developing countries as part of its US\$ 610 million cuts to foreign aid. The timing, well into the 2013–14 financial year, is described as almost as damaging as the cuts, because funding is withdrawn from initiatives that are already underway. The aid agency Oxfam says it must now consider which critical work it can no longer do. Australia will cut funding to humanitarian, emergency and refugee programs, plus contributions to the UN, Commonwealth and other international organizations eg, WHO and UNI-CEF. Australia will no longer commit to a timeline for contributing 0.5% of its GNP to overseas aid – part of its MDG commitment. (*Brisbane Times*, 18 Jan 2014) ▶ Former Australian Prime Minister Julia Gillard is the new head of the Global Partnership for Education, which works towards getting 57 million children into school and has allocated more than US\$ 2.8 billion to education. Ms Gillard is concerned about the 6.3% fall in aid spending for basic education from 2009 to 2011, as the latest UN figures show 57 million children are not in school, and 250 million children lack basic numeracy and literacy skills. She hopes that Malala Yousafzai, the UN Special Envoy for Education shot by the Taliban for demanding girls' education, will raise the profile of the global state of education. (*Sydney Morning Herald*, 11 Feb 2014)

China

China's air pollution was the worst for 52 years, with 13 provinces hitting record high levels and nearly half of China being affected by smog. There are increased efforts by government, laboratories and universities to work collaboratively in understanding the causes of air pollution and how it is dispersed or concentrated in the atmosphere. China's five year action plan aims to improve technology, planning and regulation, and emphasises making polluters pay, rewarding energy efficiency, conservation, and reduction efforts. China is applying existing technologies more extensively, leading to cleaner emissions from power stations, cleaner heating systems and more recycling of agricultural waste. Air pollution is a serious health risk but there are intensive efforts to improve air quality, with funds to subsidise environmentally-friendly industries, improved policies on pricing and taxation, and encouraging investment in air pollution control technology. (The Guardian, 18 Dec 2013)

>> China is expected to become the world's second–largest pharmaceutical market by 2016, fuelled by an ageing population, expanding public health insurance and the increasing demands of a wealthier society. However, even cheap generic drugs are much more expensive than their international benchmark. This is caused by doctors being underpaid, leading to them making up their income by drug prescriptions; and hospitals, with few available revenue streams, can charge a 15% mark-up on medicines. Medicines now comprise 40% of total health expenditure, compared to the 16% OECD average. Promoting the use of cheaper generic drugs is difficult, partly because scandals involving unsafe food and drugs make many patients and doctors favour expensive foreign-brand drugs. Efforts to promote cheaper drugs by requiring hospitals to buy them through bidding have largely failed, and indeed may have caused a shortage of some lifesaving drugs. (The Economist, 1 Feb 2014)

Smog is not the only deadly air pollutant in China, as 300 million adults smoke and 700 million people are ex-

A study shows that Australia's mass human papillomavirus (HPV) vaccination program is working, and fully vaccinated women are much less likely to develop cervical cancer. HPV can also cause penile, anal, cervical, vulvar and vaginal cancers, and genital warts. The vaccine halves the risk of cervical cancer by preventing infection by two types of HPV, saving lives and minimizing future health expenditure. However, regular smear tests are still vital, as the vaccine does not protect against other HPV strains. (*The Guardian*, 4 Mar 2014)

posed to passive smoking. China is the world's largest tobacco market and an estimated 100 million people will die from smoking–related illnesses this century. This has led to the government taking some measures, including a partial smoking ban. However, these have had little impact, and studies show that tobacco damage is set to rise. Even the proposed beefed–up measures are inadequate, and the tobacco industry is very closely linked with government. If proper anti–smoking measures (eg, health education, heavy taxation, widespread smoking bans, quitting schemes etc.) were in place, an estimated 13 million lives would be saved, and 154 million "life years" gained. The industry is largely self–regulated and its tax revenue support government finances, making more stringent actions unlikely. (*The Economist*, 1 Mar 2014)

▶ China, with more than 10% of all tuberculosis (TB) cases, is a major contributor to the global TB pandemic. However, it has halved its TB prevalence, with rates falling from 170 to 59 per 100000, and the WHO says other countries could use a similar approach. Between 1990 and 2000, TB levels fell where the WHO–recommended programme of rapid detection and treatment was implemented, and by 2010 prevalence fell by 57%, tripling this reduction. The 2014 World Health Assembly will look at setting new targets for prevalence reduction and TB elimination. However, nearly 4000 people die each day from TB, and 3 million cases go undiagnosed each year. (*BBC News*, 18 March 2014)

▶ China recently set up the alliance of Organ Procurement Organisations (OPO), to improvement the management of organ donations. The OPO chairman, Huang Jiefu, has been progressing reform in the nation's organ donation and procurement systems. Each year, approximately 300000 people need an organ transplant, but only 10000 are carried out due to a shortage of donors. Across China, only 169 hospitals are authorized to carry out transplants. (*Xinhau*, 20 Mar 2014)

Europe

>> European countries are accused of profiting from their aid budgets, by increasing the amount given as loans, often with high interest, which are classed as Official Development Assistance (ODA). The European Network on Debt and Development (EURODAD) calls for urgent reform, as these loans cost developing countries US\$ 828 million each year, reducing resources for desperately poor people. EU-RODAD calls for avoiding loans unless they have a positive impact, and donors should not be incentivised to give loans if grants are preferable. (*The Guardian*, 16 Jan 2014)

>> The UK will spend US\$ 3 billion on the economic development of poor countries in 2015, more than double the amount in 2012–13. It will continue with traditional aid programmes (eg, disaster relief, disease) but will shift future resources towards economic development, particularly growth and jobs. This coherency is a shift from its previously *ad hoc* approach. Examples of the new "smart aid" include providing technical support to improve Nigeria's power supply, and modernizing Mombasa, east Africa's largest port. The UN is concerned that high rates of Africa's economic growth rates have not translated into job creation, and NGOs call for the UK government to ensure that projects to boost trade help, not hurt, poor people. (*The Guardian*, 27 Jan 2014)

>> In Scotland, male alcohol—related deaths are double that of the rest of the UK, the cirrhosis mortality rate is one of the highest in Western Europe, and alcohol—related problems cost US\$ 1.7 billion a year. Between 1980 and 2005, alcohol became 62% more affordable with a corresponding rise in consumption, thus making a strong case for price intervention. In 2012, the Alcohol Minimum Pricing (Scotland) bill was passed by the Scottish Parliament, but was immediately challenged by the Scotch Whisky Association. Meanwhile, the bill is in limbo until the ongoing legal disputes are resolved. (*BMJ*, 6 Feb 2014)

►> Analysis by the Institute of Cancer Research (ICR) and Innovative Therapies for Children with Cancer shows that children with cancer are denied new, potentially life–saving, drugs because EU rules allow companies to trial some drugs only in adults. Drug companies can gain exemption from testing in under–18s, even if the drug may work in children, if the adult cancer does not occur in children. However, many modern drugs are targeted at genetic features of the cancer that can be common to different types of adult and child cancer. This causes delays in drugs becoming available for children, and some may never be licensed. The ICR calls for urgent reform to enable more drug–testing in children, and for more financial incentives for drug companies to develop drugs for small patient populations. (Institute of Cancer Research, 10 Feb 2014)

>> The International Monetary Fund is near to agreement with Ukraine on an aid package worth US\$ 14–18 billion over the next two years, which will potentially unlock a further US\$ 10 billion of loans from the EU and the US. It is tied to an economic reform program, including cuts to energy subsidies that could see a 50% increase in domestic gas prices, and restructuring the state–owned energy company, whose deficit is nearly 2% of GDP. Ukraine's new Prime Minister warned that the economy could contract by up to 10% in 2014 without these austerity measures. The IMF will review Ukraine's anti–corruption, tax and legal frameworks – currently it is listed at 144 out of 177 countries in an international ranking of corruption perception. (*BBC News*, 27 Mar 2014)

India

▶ Despite its reputation for being unwelcoming to foreign businesses, international fast—food chains are being welcomed in India by a young, upwardly mobile population. The spending power of this group is rapidly increasing, as more people, particularly women, enter the workforce and people acquire new tastes. The Indian market for chain restaurants is an estimated US\$ 2.5 billion in 2013 and expected to grow to US\$ 8 billion by 2020, driven by the growth of fast—food restaurants. However, health experts are concerned about the impact of public health, although businesses have encountered little public opposition as they are not perceived as replacing traditional eateries. They all face challenges of adapting their products to local customer needs without compromising their core product. (*New York Times*, 8 Jan 2014)

▶ India has reached a major milestone in the eradication of polio as its last recorded case occurred three years ago, putting it on course to be polio-free by March 2014. The fight against polio was made more difficult by the problems of poverty, dense population, poor sanitation, high levels of migration and a weak public health system. In 2012, the WHO declared India free from active endemic wild polio transmission. The victory against polio is India's second major health achievement, after the elimination of smallpox in 1980. However, there are concerns that polio may re–enter India from Pakistan, where cases have been reported. (*The Guardian*, 13 Jan 2014)

▶ India launched its national adolescent health strategy with the support of the UN Population Fund. A fifth of India's population is aged 10–19, so the benefits of a healthier youth will have a profound impact on the entire population, and is an investment in the future workforce, parents and leaders. The strategy will provide health, information and services aimed at adolescents, including girls and marginalised groups. Investing in this group could result in a demographic dividend – the accelerated economic growth that can result from a rapid decline in a country's fertility rate coupled with smart investments in health, education and job creation. (*UN Population Fund*, 17 Jan 2014)

▶ India's 2014 general election will be the largest democratic event in history, with more than 814 million people entitled to vote to decide the country's 16th government. Polling begins on 7 Apr, and ends on 12 May with the result decided by 16 May. The election's sheer scale is unprecedented; in nine polling days spread across five weeks, the world's largest electorate will visit 930 000 polling booths to cast their votes using 1.7 million electronic voting machines. For the first time, voters can select "none of the above", allowing them to reject parliamentary candidates. The impact of the youth vote and technology will be scrutinised: 24 million 18–19-year olds will participate in an election where social media and internet campaigning have featured heavily. Campaigning costs are high too, as the incumbent government faces a closely–run election and possible defeat. (*The Diplomat*, 13 Mar 2014)

▶ Six Indian innovators were selected to contribute to the development of sanitation solutions as part of the Reinvent the Toilet Challenge (RTTC): India. This India–specific program is modeled on the Gates Foundation's global RTTC, and is a collaborative effort to develop innovative, safe and affordable sanitation technologies, and to drive research, development and production of "next generation toilets." The grants were announced at the event fair, which was co–hosted by the Indian Government and the Gates Foundation. The fair was an opportunity for the 16 RITTC grant–holders to show–case progress to date and their project prototypes. (*BMGF*, 22 Mar 2014)

The Americas

▶ The Canadian Supreme Court unanimously struck down the country's anti-prostitution laws, following a challenge brought by current and former sex workers. Prior to this, selling sex was not illegal, unlike brothel keeping, soliciting, or living off the earnings from sex work. In striking down the law, the Court recognized that its provisions prevented people engaged in a risky, but legal, activity from taking steps to protect themselves. The decision gives the Canadian Government one year to devise new legislation on sex work. (*BBC News*, 20 Dec 2013)

▶ Nicaragua is the first country to ratify the Protocol to Eliminate Illicit Trade in Tobacco, the world's first international public health treaty. It aims to eliminate all forms of illicit trade in tobacco, and to co–operate internationally on this issue. Colombia, Costa Rica, Ecuador, Panama and Uruguay have also signed the protocol and are expected to ratify it soon. It must be signed by 40 countries before it can enter into force. An estimated 10% of the global cigarette trade is illicit, posing serious public health risks as it makes tobacco cheaper and more appealing to vulnerable groups such as youngsters and poorer people. It also causes revenue losses to governments. In the Americas, 16% of deaths amongst people aged 30 years and older is attributable to smoking; the joint highest in the world alongside Europe. (*PAHO*, 16 Jan 2014) ▶ The last reported case of endemic transmission of measles in the Americas was in 2002, and measles deaths have disappeared from the region. This makes the Americas the first region globally to eliminate measles – a leading cause of death for young children. Key reasons include high vaccination coverage and the early detection of cases. The WHO/PAHO measles elimination strategy was based on experience gained in polio eradication: national vaccination 'catch-up' programmes targeted at children; strengthening routine immunisation services; and mass follow-up campaigns. However, there are imported cases so vigilance is needed to avoid reintroduction and any outbreaks of the disease. (*PAHO*, 10 Feb 2014)

▶ There was a reported 43% drop in obesity rates amongst children aged 2–5 years in the USA; the first indications that obesity trends in America's youngest children may be turning a corner. Approximately 8% of children in this group were obese in 2012, down from 14% in 2004. It is the first evidence of any obesity declines amongst any age group, and bodes well for the future as obesity becomes established at this age, and can be very difficult to shake off in later years. However, this is still a very small percentage of the American population, and obesity rates in the rest of the population have remained constant; even increasing for women aged over 60. Possible reasons for the decline include less consumption of sugary drinks, higher rates of breastfeeding, less calorie consumption amongst children, and the impact of anti–obesity programmes. (*New York Times*, 25 Feb 2014)

>> The end of March 2014 was the deadline to sign up for health insurance under the US Affordable Care Act, also known as "Obamacare". It will be some time before it is known how many people have signed up for coverage, but already some things are clear. First, more people have coverage in part due to the 26 states that have expanded Medicaid, and thus covering millions of poor adults. However, coverage is far from universal with half of all states not expanding Medicaid coverage, and serious glitches in the online health insurance system has led to enrolment problems. The importance of young, fit people purchasing insurance to help pool risk may be over–stated, as Obamacare contains mechanisms to smooth risk until 2017, and companies have limited time to set their rates for 2015. (*The Economist*, 31 Mar 2014)

• The Bill and Melinda Gates Foundation

▶ Billionaire Warren Buffett donated US\$ 2.6 billion of Berkshire Hathaway Class B shares to the Bill and Melinda Gates Foundation, plus four charities linked to his family. The "Oracle of Omaha" is a notable philanthropist who has been giving annually to the foundation since 2006, with an estimated total donation of US\$ 1.5 billion in shares. It exceeds Mr. Buffett's last contribution, when he donated US\$ 1.52 billion in 2012. He has pledged to give away 99% of his fortune upon his and his wife's demise. By 2012, he inspired 83 fellow billionaires to make similar pledges, agreeing to give away at least half their fortunes during their lifetimes. (*Forbes*, 8 July 2013)

▶ Russian investor Yuri Milner, a physicist by training, is looking to apply his scientific approach to philanthropy. He is one of seven billionaires to recently sign the Giving Pledge, which commits its current 122 signatories to giving at least half their wealth to charitable organizations. As well as encouraging philanthropy amongst the world's wealthiest, the Pledge, founded by Warren Buffet and Bill and Melinda Gates, aims to inspire others towards giving and sharing knowledge. "In this season of giving, we are inspired by the millions of people across the global who give what they can in meaningful and significant ways. The Giving Pledge is rooted in this spirit, and hopes to inspire people to tackle problems that are inherently difficult and diverse in an effort to address the pressing social problems they care about most," says Melinda Gates. (*Forbes*, 10 Dec 2013)

▶ The BMGF named its new Chief Executive as Susan Desmond–Hellman, the chancellor of the University of California, San Francisco (UCSF), and an oncologist and public health expert. She took up the post on 1 May 2014. Prior to UCSF, she was president of product development at biotech pioneer Genentech, where she led the development of two of the first gene–based cancer drugs, Herceptin and Avastin. (*Reuters*, 17 Dec 2013)

▶ In an interview with the Wall Street Journal, following the Foundation's "2014 Open Letter", Bill and Melinda Gates spoke about the state of today's world - better today by nearly all measures. They debunked three myths on the world's poor. First, poor countries are not doomed to stay poor; more than half the world's population lives in a new class of middle-income countries, and they predict that there will be almost no poor countries left by 2025. Second, foreign aid investment is a huge success by saving lives and founding long-term economic progress; it is not a waste of money, and potential corruption should not deter donors. Finally, saving lives does not cause over-population; instead falling death rates cause falling birthrates. There is a greater chance of creating a world where extreme poverty is the exception not the rule, if these myths are less widely believed. (Wall Street Journal, 17 Jan 2014)

▶ In a wide-ranging conversation with the American Enterprise Institute, Bill Gates spoke about falling global poverty and child mortality rates, the developmental challenges faced by African countries, the role of government and philanthropy in addressing market failures, the US education system, the Foundation's priorities, and how to measure the impact of aid. He talked about the importance of the private sector in African agriculture, as farmers above the subsistence level can provide better diets for their children, with more resilience during hardship. He advised on how people can make a difference by focusing on a small number of causes, be engaged with them, and stay with them long-term. He shared his views on the long-term trends in the jobs market, saying that more jobs are likely to be automated, and called for reforms to the tax system by switching taxation from payroll to consumption and capital to increase demand for labour. (American Enterprise Institute, 13 Mar 2014)

• The GAVI Alliance

▶ The 2013 *Publish What You Fund* index ranks the transparency of donor organisations, by commitment to aid transparency, organisation–level publication of financial information and general plans, and the availability of country–specific project activities; and 2013 saw the format of publishing feature in the rankings. The index is restricted to influential donors which spend over US\$ 1 billion a year, and must be committed to transparency. The leaders in aid transparency were the USA's Millennium Challenge Corpo-

ration (strong in publishing information in machine–readable formats), the UK's Department for International Development (where transparency is part of its agenda), and GAVI Alliance (the only agency to publish all information in a machine–readable format). (*Devex*, 24 Oct 2013)

▶ The US has committed an additional US\$ 175 million to funding GAVI vaccination programs; a record amount for the US government and comes as GAVI prepares for its 2016–20 funding replenishment. GAVI has undertaken an

Agencies

unprecedented acceleration of its programs, from 55 rollouts in 2011–12 to more than 150 in the following years, including the inactivated polio virus. Ensuring that the benefits of vaccination reach every child is an important focus of the next cycle. (*GAVI*, 17 Jan 2014)

▶ At the World Economic Forum at Davos, GAVI announced a US\$ 152 million initiative to immunise children against disease using private sector partnerships, which leverages cash and expertise from corporations and foundations. These partnerships have a critical role in improving global health, and there were calls for increased participation from the private sector to reach the 22 million children who go unvaccinated annually. "Every 20 seconds, a child dies from preventable diseases," said Ms Justine Greening, Britain's international development secretary. (*GAVI*, 28 Jan 2014)

▶ GAVI announced its support of vaccination programmes in Rwanda, Uganda and Uzbekistan, to protect 1.5 million girls against the causes of cervical cancer. The first national roll–outs will begin in Uganda and Uzbekistan in 2015, while Rwanda moves from a vaccine manufacturer's donation to GAVI support to secure its existing programme. Cervical cancer was described by GAVI as a "scourge" on women and their families in developing countries, where limited screening and treatment make vaccination a vital prevention tool. These countries have developed detailed plans to ensure that girls aged 10–12 years are vaccinated in schools, and that girls not in education are included reached via community outreach. (*GAVI*, 8 Mar 2014)

Rotavirus vaccines have been introduced into Cameroon's routine immunisation programme, with support from the GAVI Alliance. This life-saving virus could have a massive impact on children's health, as each year rotavirus claims almost 6000 lives and causes an estimated one-third of all diarrhoeal hospitalisations in Cameroon in children aged under five. Cameroon would have a greater chance of reaching the Millennium Development Goal of reducing child mortality if every child is fully vaccinated with the recommended vaccines before their first birthday. "Rotavirus vaccine is a very effective way of protecting children against rotavirus diarhoeal disease and can be used in addition to other general diarrhoea prevention methods including hand washing with soap, drinking potable water and using latrines," said Dr Charlotte Faty Ndiaye, WHO representative in Cameroon. (GAVI, 28 Mar 2014)

• The World Bank

▶ A coalition of developed and developing countries pledged to accelerate efforts to end extreme poverty, by committing a record US\$ 52 billion to the World Bank's International Development Association. There will be more emphasis on challenging frontier areas and private sector mobilisation, and investment in gender equality and climate change is key to the future; all is underpinned by a commitment to equitable growth. Amongst others, the support will provide eg, electricity for 15–20 million, vaccines for 200 million children and extend basic health care and clean water supplies. It will run from 2014 to 2017, thus spanning the MDG and post–2015 agenda. (*World Bank*, 17 Dec 2013)

▶ Cambodia has exceeded the Millennium Development Goal's poverty target, and is one of the best global performers in poverty reduction. The share of people living in absolute poverty (US\$ 1.15/d) fell from 53% to 20.5% between 2004 and 2011. The main drivers were increased rice production and prices, with resulting higher revenue and wages. However, most people still live too close to the poverty line, and decreasing numbers of people in absolute poverty has led to a sharp rise of "near–poor" people, from 4.6 million in 2004 to 8.1 million in 2011. Small income shocks (eg, a loss of US\$ 0.30/d) could throw 3 million back into poverty. Cambodia's development goals focus on helping the remaining 20% escape absolute poverty, and prevent the near–poor from slipping back, emphasizing growth and equity. The Bank recommends infrastructure improvements, broadening access to education and health services, and reducing child malnutrition as key to lifting more people out of poverty. Crop diversification and enhanced rice profitability will help prevent the near–poor slipping back into absolute poverty. (*World Bank*, 19 Feb 2014)

>> The World Bank has delayed approving a US\$ 90 million loan to support Uganda's health system. The Bank's President, Mr Jim Kim, said that the Bank is reviewing wherever recent changes in Ugandan law would lead to discrimination against gay people in the maternal and family planning projects it supported. He stressed that it will continue to help fight poverty in Uganda. The Bank has previously used this tactic to express concerns about human rights, eg, freezing loans to China after Tiananmen Square. "Anti–discrimination and equality might be part of our moral values as individuals, but for us the even more important thing is now we've got a lot of good data that suggests it's bad for economic growth too," says Mr Kim. (*Devex*, 14 Mar 2014) ▶ Tackling the pervasive inequality faced by women farmers in Africa is vital to tackling poverty, increasing economic growth and feeding its population. A World Bank report examined the scale and differences between male and female farmers in six African countries, identifying gender gaps, factors holding back female farmers, and actions to reduce inequality. It found that female farm productivity is 13–25% lower than male in the countries surveyed. It estimates that given equal access to resources, women farmers could increase farm yields by 20–30%, thereby improving food security, economic growth and creating job opportunities for millions of young Africans. The report calls for governmental action to close the gender gap, eg, by improving female land rights, use of agricultural techniques, education, and market and childcare access. (*World Bank*, 18 Mar 2014)

▶ The World Bank, The Gates Foundation and other donors are increasing efforts against neglected tropical diseases in low–income countries with a US\$ 240 million injection of new funding. This follows a pledge two years ago by several pharmaceutical companies (Sanofi, GlaxoSmith-Kline, Merck etc.) to donate medicines to tackle parasitic and bacterial infections that threaten 1–in–6 people worldwide. Half of the funding will be spent on combating soil– transmitted helminthes – intestinal worms that commonly affect children living in poverty. The World Bank Group has also committed US\$ 120 million to support the fight against neglected diseases, including school–based worming programmes. (*Reuters*, 2 Apr 2014)

• United Nations (UN)

>> The Lancet published reflections on the UN General Assembly on delegates' wish to focus on MDG successes, rather than on learning from missed opportunities. Three lessons already apparent from the MDG agenda were outlined. First, MDGs have created a vast aid industry that can cause duplication and confusion without a sustainable legacy. Second, unacceptable inequities in health will persist and worsen unless a proper financing facility is created. Lastly, short–termism has incentivized interventions that can be deployed and measured quickly, whilst overlooking the need for skilled health workers, accurate information and quality care in health care. (*The Lancet*, 5 Oct 2013)

▶ At its 68th session, the UN General Assembly adopted a US\$ 5.53 billion budget to finance its activities over the next two years, including its global judicial, humanitarian and peace-keeping operations. It also adopted more than 20 texts on a range of issues, eg, financing international criminal tribunals. Of particular note was the State of Palestine casting its first ballot, one Member State declining a seat on the Security Council, and remembrances of Nelson Mandela highlighting the world's need for peacekeepers. The post-2015 development agenda is the proposed theme for the general debate, with several high-level thematic debates scheduled for 2014, to be concluded with a stocktaking event in September. (*UN News*, 27 Dec 2013)

>> Research by the University of Kent shows that more than 70% of religious NGOs at the UN are Christian, and the Vatican has special observer status as both a state and religion. Islam is represented via a collection of states rather than civil society NGOs, and Asian religions (eg, Buddhism, Hinduism) are unrepresented, with funding being a major barrier to access. It found that the overall number of inter–faith and new–age NGOs is small but they can have a disproportionate influence, having many meetings with UN diplomats. It calls for more awareness, transparency and equality in how religious NGOs work in the UN, and more understanding of how religions enhance and constrain human rights. (*The Guardian*, 1 Jan 2014)

>> The UN has released early results from its far-reaching global survey MyWorld2015. The ongoing survey asks people which factors would improve their and their families' lives. Results will be shared with the Secretary General and others leading up to the post-2015 development agenda. Early results suggest that education is a main priority for two-thirds of respondents, and health is a priority for those aged over 61. Otherwise, priorities tend to be specific to circumstances and countries. However, climate change action scores poorly. Although this may be caused by the question's wording and could change, it is concerning to those hoping to combat climate change by individual action, as it seems many are not interested. (*The Washington Post*, 20 Feb 2014)

>> The UN faces a lawsuit over the cholera outbreak in Haiti that is blamed on its peacekeepers. The UN does not accept responsibility for the outbreak, which has killed more than 9000 people. The lawsuit alleges that the outbreak arose from "negligent, reckless, and tortious conduct", beginning after the arrival of UN troops after the 2010 earthquake who were not screened for cholera. The UN hired a private contractor to ensure sanitary conditions, however contaminated sewage leaked into water supplies, resulting in Haiti's first cholera outbreak for 150 years. The UN claimed immunity, but the lawsuit argues that the UN is not immune from liability in such cases. (*The Guardian*, 12 Mar 2014)

• UN AIDS and The Global Fund

The WHO says that millions of young people are at risk of HIV infection due to inadequate health services, as AIDSrelated deaths increased by 50% amongst 10-19 year-olds from 2002 to 2012, despite falling by 30% amongst the general population. This is ascribed to government failures in prioritising adolescents in national HIV plans, lack of teenfriendly testing services and counseling, plus inadequate treatment of people who are born with HIV. WHO have issued new guidelines on HIV support and care for adolescents, calling for more tailored services, immediate treatment, and support for status disclosure and treatment compliance. WHO calls for action to tackle barriers to HIV treatment and prevention, and other groups call for a "prevention revolution," particularly amongst young people and marginalised groups, to accelerate the global fight against HIV and AIDS. (The Guardian, 26 Nov 2013)

>> The world's donor countries pledged US\$ 12 billion over three years to the Global Fund to Fight AIDS, Tuberculosis and Malaria. Although an increase over the 2010 pledge, it falls short of the hoped-for US\$ 15 billion. US\$ 15 billion would help 85% of people in need; US\$ 12 billion would reach 68%. The goal of ensuring that the increasing numbers who test positive for HIV receive treatment will not be met at this donation level, the ongoing battle against malaria needs more investment if malaria deaths are to hold steady yet alone further fall, and tuberculosis is rising in line with the number of HIV cases because people with compromised immune systems are more vulnerable to it. Reactions on the pledge were divided; some advocates are pleased that donations have increased, whilst others call for rich countries to contribute more. (New York Times, 3 Dec 2013)

▶ An outsider could perceive that the UN's global health agencies are confused and complex, argues Jon Lidén, Centre on Global Health Security, and other agencies, such as NGOs and Foundations, are perceived as more responsive and innovative. Against this background, UN agencies are discussing major structural reforms. However, much of the progress in global health in the past decade could not have happened without the UN agencies, and for some areas (eg, accident and violence prevention etc), there are no alternatives. He argues that, aside from UNAIDS's Michel Sidibé, the UN lacks new ideas, vision and leadership. The UN is most effective when its leaders set bold agendas for others to follow, rather than second–guessing member states' priorities and worrying about other agencies' activities. (*Chatham House*, 18 Dec 2013)

Bangladesh has a history of endemic malaria transmission in many districts. The Global Fund gave funding to the Bangladesh National Malaria Control Programme, and there was a follow-up epidemiological and economic assessment of the country's malaria control. It uncovered a general reduction in malaria cases, mainly due to the widespread use of nets, more use of rapid diagnostic tests and antimalarial treatments, and a high number of health workers and facilities. Insecticide-treated nets were cheaper, making the preventative measures highly costeffective. Bangladesh is now moving from control to elimination in some districts, making total elimination an achievable prospect. However, consistent funding is essential to avoid the inevitable resurgence if control and surveillance efforts are scaled back. (The Lancet Global Health, 1 Feb 2014)

>> Studies show that intimate partner violence can increase the risk of HIV infection by 50%, and that one—in—three women experience intimate partner violence at some point. Violence, or fear of violence, can undermine access to treatment, care and support services for women living with HIV. UNAIDS has called for governments and communities to take action against violence against women, arguing that it is not only a human rights violation, but also makes them more vulnerable to HIV infection. Women living with HIV are more likely to be subjected to violence, women most vulnerable to violence are also most vulnerable to HIV, and violence undermines the HIV response by creating a barrier to accessing services. (UNAIDS, 12 Mar 2014)

UNICEF

>> The EU announced a US\$ 431 million allocation to UNICEF to improve maternal and child health and nutrition in 15 developing countries. It will focus on under—nutrition and infectious diseases – among the root causes of child mortality – and other programmes will focus on im-

proving access to water, sanitation, medical services and nutrition. This builds on achievements towards the MDGs, and accelerates progress towards MDG4 – reducing mortality in children under 5 years by two-thirds – which otherwise will not be reached until 2028. UNICEF and the EU, in partnership with governments and other agencies, will scale–up interventions to reduce child mortality and improve maternal and pre–natal health. (*UNICEF*, 4 Feb 2014)

>> UNICEF's report, *Every Child's Birth Right: Inequities and Trends in Birth Registration*, found that in 2012 only 60% of newborns were registered, equating to unregistered 230 million children aged under 5 world–wide. These children are at risk of being unable to access government programmes such as education and health care, are more vulnerable to neglect and abuse, and in the longer–term it may affect their citizenship and right to vote. Children in certain groups or in impoverished or remote areas are less likely to be registered. UNICEF is developing low–cost technology to identify and report unregistered births, working in countries to register newborns and bring them into existence in the eyes of government. (*TIME*, 10 Dec 2013)

>> UNICEF appealed for US\$ 2.2 billion to provide essential humanitarian aid in 2014 to 85 million people, including 59 million children, who face conflict, natural disasters and other emergencies across 50 countries. UNICEF said that the children and families displaced by conflict in South Sudan join millions more affected by conflict in the Central African Republic and Syria. However, many other desperate situations with less media focus need immediate funding and urgent aid, eg, Afghanistan, Colombia, the Democratic Republic of the Congo, Myanmar, Somalia and Yemen. For Syria and the sub–region, UNICEF is appealing for US\$ 835 million to deliver life–saving assistance including immunisation, water, sanitation, education and protection, and to investment in sustainable futures. UNI- CEF is also seeking funds that are not earmarked for specific projects, to enable it to respond to underfunded emergencies or where needs are greatest. (*UNICEF*, 21 Feb 2014)

>> The Philippines is gradually recovering from the Nov 2013 Typhoon Haiyan, shown by health centres re–opening, improved supplies of clean water, and children returning to school. Yet children's needs remain great, and visible destruction is a reminder that much needs to be done to restore devastated lives and communities. Despite intense relief efforts with significant achievements, recovery is likely to be protracted. UNICEF and its partners are focusing on efforts to improve community resilience, providing urgently needed humanitarian assistance and restoring essential services. It has also strengthened its monitoring and information systems on supply inputs, distribution, results and quality. (UNICEF, 7 Mar 2014)

▶ UNICEF is distributing 150000 mosquito nets and accompanying educational materials, to 75000 displaced people in the Central African Republic ahead of the impending rainy season, which brings the threat of malaria – particularly deadly to vulnerable populations. Before the crisis, only 36% of the country's children slept under a mosquito net, and children in displacement sites in makeshift dwellings are particularly at risk from malaria. Since the start of the conflict, malaria has caused an estimated 40% of all illnesses in children aged under 5 years, and sleeping under a mosquito net reduces malaria deaths by 20%. UNICEF partnered with the National Red Cross for the distribution, overseen by the Ministry of Health. (UNI-CEF, 14 Mar 2014)

• World Health Organization (WHO)

Since 2000, control measures have prevented 3.3 million deaths from malaria, cutting its death rate by 45% (50% in children under five), mainly within the 10 countries with the highest malaria burden. This is a huge pay– off for malaria control and prevention measures. However, WHO stated that absolute numbers are not reducing as quickly as they could. Funding cuts could hinder progress, although agencies recently announced the provision of over 200 million nets over the next 12–18 months. (*Reuters*, 11 Dec 2013)

>> The WHO's *World Cancer Report* reveals the alarming rise in the global cancer burden and the urgent need for effective prevention strategies. There was an estimated 14 million new cases in 2012, which is expected to rise to 22 million by 2022. Cancer deaths are expected to increase

from 8.2 million annually to 13 million. Developing countries are disproportionately affected, with 60% of cases and 70% of deaths. Access to effective and affordable treatments would reduce mortality, but is a huge strain on health care systems as the annual economic cost of cancer is an estimated US\$ 1.16 trillion. However, vaccination against hepatitis B and HPV, reducing tobacco usage and promoting physical activity and obesity reduction can markedly reduce cancers linked to infections and lifestyle. Low–tech screening and early detection can be highly cost–effective interventions, and the WHO calls for governments of developing countries to enforce regulatory measures and implement cancer prevention plans. (*WHO*, 3 Feb 2014)

>> New mortality estimates show that annual measles deaths have reached new lows, dropping 78% from more

than 562 000 in 2000 to 122 000 in 2012, with an estimated 13.8 million lives saved by vaccination. Global measles immunisation coverage is a stable 84%, and the Measles and Rubella Initiative has supported mass vaccination campaigns. However, progress towards measles elimination is uneven, with some populations still unprotected and measles is still a global threat. Routine measles vaccination coverage is important in reaching the MDG for child mortality because of its potential to reduce child mortality without improved immunisation coverage, outbreaks will continue. The ability to contain outbreaks by improving coverage and, when necessary, implementing high quality vaccination campaigns, requires countries to place a high priority on elimination goals and to invest heavily in health systems improvements. (*WHO*, 6 Feb 2014)

>> The WHO's global action plan set a target for a 25% reduction in non–communicable diseases (NCDs) by 2025; the "25×25" strategy. The plan lists nine voluntary national targets –reducing mortality from NCDs, halting the rise of diabetes and obesity, and other on reduced alcohol intake, smoking and salt, plus more exercise, better blood pressure control and improved treatment. An analysis of the strategy (published in *The Lancet*) calls for NCDs to be measured by mortality and morbidity, thus broadening the range of conditions identified in the strategy (cardiovascular disease, diabetes, cancer and chronic respiratory disease) to include eg, neurological and musculoskeletal diseases. This more comprehensive approach recognises that NCDs can be caused by factors outside individuals' control (eg, air pollution, environmental and time constraints due to poverty that don't allow for exercise), so tackling them means action at both societal and individual levels. (*The Lancet Global Health*, 3 Mar 2014)

According to the WHO, air pollution kills 7 million people globally each year. Fumes from indoor stoves cause half of all deaths – with women and children having higher exposure, as they spend more time indoors – according to the WHO. It causes 1–in–8 deaths and is the biggest environmental health risk. One of its main risks is tiny particles can get deep into the lungs, causing irritation and possibly heart problems. WHO has classified air pollution as a carcinogen, linked to lung and bladder cancers. Experts call for more research on the most dangerous components of air pollution to more effectively target control measures, and individuals can limit their exposure by avoiding travelling at rush hour and taking quieter roads; however there is little evidence that face masks provide protection. (*Associated Press*, 25 Mar 2014)

Demography

▶ The wealthy eastern province of Zhejiang is the first to implement a relaxation of China's one-child policy, allowing more parents to have a second child. This is part of a plan to raise fertility rates and ease the financial burden on China's ageing population. It allows couples to have two children if one of the parents is an only child; previously a couple could only have a second child if both parents were only children. Government figures showed that this policy, which covers 63% of the population, has averted 400 million births since 1980. (*Reuters*, 17 Jan 2014)

▶ Life expectancy in India has increased by five years in a decade, to stand at 67.3 years and 69.6 years for men and women, respectively. This increase is attributed to improved immunisation, nutrition, and prevention and treatment of infectious diseases. Maternal and infant mortality rates have fallen to 212 and 42 per 100 000, from 301 and 58 in the past decade. However, increasing life expectancy beyond 70 years depends on environmental factors (eg, clean drinking water) and better control of non–communicable diseases. Some experts sound a note of caution, noting that increased life expectancy would increase the disease burden. (*Times of India*, 29 Jan 2014)

▶ A recent study shows that the fertility rate of much of Africa is falling more slowly than expected, meaning that the continent's overall population will rise sharply, its big cities will grow alarmingly, and there is an impending "youth bulge". 78% of Africa's people live in countries still transitioning to low mortality and fertility. There were 411 million children in 2010, with a predicted increase to 839 million in 2050. Although there will be lots of new entrants into the labour market, educating them will be expensive, and the continued reliance of precarious employment for young workers is worrying. It is argued that African governments must make more effort to spread the use of contraception, which is low by international standards. Without this, Africa risks having too many people with too few chances to escape poverty. (*The Economist*, 8 Mar 2014)

▶ China has revealed plans for state-led infrastructure construction, as it moves 100 million more people from rural areas to growing cities. The "National New-Type Urbanisation plan" details a massive building programme of transport networks, infrastructure and residential real estate, and China's leaders hope that this will boost China's flagging economic growth by boosting domestic demand. The plan aims to increase China's urbanisation rate to 60% by 2020. However, this goal is complicated by China's strict household registration system, which makes it difficult for those born in the countryside who move to the city to register for permanent resident status in the city. Therefore urbanisation can be reversed if rural migrants move back to their village upon losing their job. (*Financial Times*, 17 Mar 2014)

▶ Japan's population fell by a record 244000 people in 2013, accelerating a trend which began in 2004, and making it the fastest-ageing society on earth. There are warnings that the country's population will fall from 127 million to 87 million by 2060, almost 40% of whom will be aged 65 or over. Mass immigration is one possible solution, but an estimated 650000 immigrants are required each year unprecedented in a largely homogenous society. Another solution is to boost fertility rates, which are amongst the world's lowest. To succeed in this, Japan needs to make it easier for women to work, and address the country's wide gender gap. Without such measures to boost its population, Japan's already-high public debt will be further strained by the cost of caring for its elderly population, and it may have to adjust to having a reduced economic and political role in the world. (The Economist, 25 Mar 2014)

Economy

>> The UN reported that the global economy will continue to grow over the next two years, but stronger international policy co–ordination is needed to steady residual fragility in the banking sector and geopolitics, which risk financial stability. Global economic growth is expected to be 3.0% in 2014 and 3.3% in 2015, compared to 2.1% in 2013. These forecasts are based on stronger–than–expected growth in the USA and an end to the Eurozone's recession, although the eurozone will still experience high unemployment and austerity. Large emerging economies, such as China and India, have avoided deceleration. There are risks ahead, including misjudgements in ending the US Federal Reserve's quantitative easing stimulus. Policy–makers need to balance an improved recovery with mitigating the effects of quantitative easing in major economies, plus advance reforms in the international financial system. (UN News, 18 Dec 2013) ▶ The world's richest 85 people (who could all fit into a bus) have a combined wealth of US\$ 1 trillion – as much as the world's poorest 3.5 billion people, according to an Oxfam report; and the wealth of the 1% richest people is US\$ 110 trillion, or 65 times as much as the poorest 50%. Oxfam is concerned that this concentration of resources threatens political stability and will increase social tensions. It fears that the wealthiest parts of the population will pass on their advantages to their children, and lock out others from equality of opportunity. It called on delegates at the 2014 World Economic Forum to tackle the problem, both by refraining from tax avoidance and using their wealth to seek political favors. (*The Guardian*, 20 Jan 2014)

▶ A study by the Center for Strategic and International Studies shows that private sector corruption in developing countries is a tax on growth that costs at least US\$ 500 billion a year – more than triple all foreign aid in 2012. Corruption distorts marketplace incentives and creates economic inefficiencies, which are not directly measurable but weaken growth and undermine confidence in government. Bribe payers are more likely to be exposed, not the officials who accept bribes, thus perpetuating the problem. It calls for research on the impact of good governance on company value; the application of new technologies to expose corruption and policy changes; and compulsory anti–corruption components in free trade agreements. (*Thomson Reuters Foundation*, 22 Jan 2014)

▶ Sub–Saharan Africa is the world' fastest–growing economy, and is undergoing a quiet manufacturing boom – almost always essential to development. Farming, services and exporting commodities still dominate, but new industries are emerging. Manufacturing's share in GDP is steady at 10-14%. Industrial output is expanding as quickly as the rest of the economy, shown by the growth of domestic and overseas manufacturers. Many are benefiting from growth outside manufacturing, eg, retail. Construction booms foster access to high-voltage power, and the spread of mobile telephone services helps small suppliers, and there is growing local demand for African app and software developers. This is underpinned by improvements in education and human capital, and spurred by investment by Chinese workers. Many jobs could leave China for Africa if labour productivity continues to rise, and corruption and red tape are curbed. Africa is in a good position to industrialise, with favourable demography, urbanisation, an emerging middle class and strong services. (The Economist, 8 Feb 2014)

►> Climbing out of, and staying out of, extreme poverty can be difficult; people can be driven back by unemployment, poor health and natural disasters, etc. A report by the Overseas Development Institute and the Chronic Poverty Advisory Network warns of poverty's "revolving door", and that progress in reducing extreme poverty may not continue. It calls for efforts to address the "three legs" of poverty: chronic poverty; becoming poor; and enabling those who have escaped poverty to keep moving up. It recommends three approaches to zero poverty: cash relief as a safety net; investment in education; and economic growth that helps the poorest by providing stable, safe and adequately paying jobs. It calls for more action on tackling chronic poverty, the addressing of which is expected in the post–2015 framework. (*Voice of America*, 10 Mar 2014)

Energy

▶ The "MINT" countries of Mexico, Indonesia, Nigeria and Turkey are the focus of attention as the next global economic powerhouses. Common factors include large populations with a high percentage of working–age adults and geographical placements allowing them to take advantage of changing world trade patterns. Individually, these countries face problems with corruption, energy demands, infrastructure and the need for reform. Their governments are tackling these problems with enthusiasm and tenacity, leading to predictions that they could join the group of the world's 10 largest economies within 30 years. (*BBC News*, 6 Jan 2014)

▶ Energy and water are crucial to human society and development. Both are tightly bound as water is needed for most energy generation; and the water sector needs energy to extract, treat and transport water. Both resources are under pressure as the global population grows towards 9 billion, leading to increases of an estimated 15% and 35% in water and energy consumption, respectively. Climate change means increased water variability and more extreme weather; decreasing water will make it harder to generate energy. To deal with these risks, the World Bank launched the *Thirsty Energy* initiative to help governments prepare for an uncertain future. "The water–energy interrelationship is critical to build resilience as well as efficient, clean energy systems. The time to act is now," says Ms Rachel Kyte, World Bank Group Vice President and Special Envoy for Climate Change. (*World Bank*, 16 Jan 2014)

Business Insider reported on Hans Rosling's talk on energy inequality, which showed how 5 billion people still

wash their clothes by hand. Hans Rosling believes that access to labour-saving devices like washing machines foster education and democracy. The middle chunk of 5 billion people (above the 2 billion of US\$ 2/d, below the 1 billion of US\$ 80/d) largely have access to electricity, but mainly wash their clothes by hand - time-consuming and hard work. He shows that the richest one billion people consume half of the world's energy, and the poorest two billion one-sixth. Economic growth could allow everyone access to energy and labour-saving devices. He believes that wealthy populations cannot dictate others' energy usage, and should concentrate on reducing their own energy consumption and implementing green energy. He showed the washing machine's impact on his own family; it meant his mother could go to the library, read books to her son and learn English. (Business Insider, 29 Jan 2014)

▶ A team of researchers at the National Ignition Facility (NIF) at the Lawrence Livermore National Laboratory in

Environment

▶ The 2013 Annual Conference of the Society of Environmental Journalists examined the media role in an era of rapid climate change, and how to communicate the interconnected stories of population, development and environmental crisis. Journalists find the global media industry does not accept stories without established paradigms, and it is almost impossible to connect the science of climate change with the human impact of those changes. In response, journalists are working with researchers and activists who view environmental justice and population as inescapably linked. An example presented at the conference is the NGO Conservation through Public Health in Uganda working with remote communities in the Bwindi Impenetrable National Park to achieve both gorilla conservation and improved access to family planning. The initiative teaches people how to prevent human/ape disease transmission, and also deploys peer educators to spread information on contraception. (Thomson Reuters Foundation, 5 Oct 2013)

▶ The International Agency for Research on Cancer (IARC) declared that air pollution is a carcinogen, ranking it as the most important environmental carcinogen ahead of second-hand tobacco smoke. Its main risk is fine particles that can be deposited deep in the lungs. It is almost impossible to avoid air pollution, which may lead governments to introduce stricter controls. In 2010, there were more than 220 000 lung cancer deaths attributable to air pollution, and there is a link with a slightly increased risk of bladder cancer. Air pollution is a particular problem in

California claim that for the first time, more energy has been extracted by controlled nuclear fusion than was absorbed by the fuel to trigger it. Although the gain was very small, this could still be a critical step towards ignition, the point beyond which more energy is generated than is put in, although fusion–energy generation is still a distant goal. (*Nature*, 12 Feb 2014)

►> Achim Steiner, head of the UN Environmental Programme, warns that shale gas could become a liability in global efforts to limit climate change. Shale gas supporters state that it can help move countries away from carbon–intensive coal as it burns more cleanly than coal with less CO₂ emissions. However, Achim Steiner believes that it will delay the vital transition from fossil to renewable fuels. Indeed, it could block progress towards low–carbon and zero–emission energy production by providing a distraction from this longer–term goal. (*The Guardian*, 26 Feb 2014)

China and India, and collective international action by governments is necessary to improve air quality. (*Associated Press*, 17 Oct 2013)

▶ High energy costs, declining competitiveness and ongoing economic weakness are causing EU policy-makers to review Europe's standards on climate-change regulation. These include tough rules on emissions and ensuring more use of renewable energy. However, the EU has now proposed an end to targets for renewable energy production, by introducing an overall goal that will probably be harder to enforce. It has reduced curbs on the environmental damage caused by fracking. Despite this, the EU introduced a 40% cut in carbon emissions by 2030. EU carbon emissions have already fallen sharply, but this is partly caused by contracting economic activity, and is subject to reversion. Environmental groups were critical of these announcements, describing them as "totally inadequate", and of ignoring the costs of dealing with climate change. (New York Times, 22 Jan 2014)

➤ At the World Economic Forum in Davos, the OECD called for leaders to tackle the huge risk posed by carbon dioxide emissions. It recognised that although many countries have made progress, current pledges on reductions are not enough to maintain a 2°C ceiling on global temperature increases. Governments must implement plans for zero net emissions from fossil fuels from 2050 onwards. This is challenging as fossil fuels account for 67% of global electricity generation and 95% of transport energy. This is compounded by shale gas being a potential source of fos-

sil fuels, investment in carbon–intensive technologies is more profitable than low–carbon technologies, and revenue from oil and gas contribute much to government revenue. The OECD calls for measures to deal with this by signaling increases in carbon prices such as reforming fossil fuel subsidies and addressing unclear and inconsistent policies. (*OECD*, 27 Jan 2014)

▶ The latest UN-backed report from the Intergovernmental Panel on Climate Change (IPCC) says that global warming is unequivocal, almost certainly due to human influence since the mid–20th century, and atmospheric concentrations of greenhouse gases – already at the highest levels for 800000 years – will persist for centuries even if emissions stop. Continued emissions will cause further warming and changes in all components of the climate system, with dangers from the melting of the Greenland and Antarctic ice–sheets, rising ocean levels and more extreme weather events. "Limiting climate change will require substantial and sustained reductions of greenhouse gas emissions," it states. (*UN News*, 30 Jan 2014)

• Food, Water and Sanitation

▶ November 19th is the UN's World Toilet Day, which highlights the massive impact of inadequate sanitation on hundreds of millions of people world–wide. Described as "the biggest global development challenge of the 21st century", one–in–three people lack access to a toilet, and diarrhoea is the world's biggest killer of children under five. This is largely preventable, and the UN estimates a US\$ 4 return for each US\$ 1 invested in sanitation, giving children a better education and reduced pressure on health budgets. (*BBC News*, 19 Nov 2013)

>> The World Bank has approved a US\$ 500 million credit to improve piped water supplies and sanitation in the Indian states of Assam, Bihar, Jharkhand and Uttar Pradesh. Only 31% of the 167 million Indian rural households have access to tap water and domestic toilets, and 67% of the rural population practise open defecation. This fits with the government's plan of ensuring that 90% of the rural population has access to piped water. The economic impact of inadequate sanitation is an estimated 6.4% of GDP. "Some 3.8 million women, who bear the burden of securing daily water supplies and dealing with illnesses from poor water and sanitation facilities, are expected to benefit from improved facilities that will be created in the project areas. The project will reduce the time spent by women in collecting water, which they can now use in other productive ways," said Ms Onno Ruhl, the Bank's country director for India. (World Bank, 7 Jan 2014)

>> The UN Food and Agriculture Organisation (FAO) called for increased efforts to improve the operation of global food systems, stating that half of the world's population is affected by under– and over–consumption of food. Despite abundant supplies, 840 million people go hungry each day, and the health of another 2 billion is compromised by nutrient deficiencies. Over–consumption increas-

es the risk of diabetes, heart problems and other diseases. Looking ahead to 2050, when the world must support 9.6 billion people, there must be more emphasis on sustainably–produced nutrient–dense foodstuffs. Increased meat consumption means that sustainable livestock management is crucial. "If the global community invested US\$ 1.2 billion per year for five years on reducing micronutrient deficiencies, the results would be better health, fewer child deaths and increased future earnings. It would generate annual gains of US\$ 15 billion – a cost–to–benefit ratio of almost 13–to–1", says Helena Semedo, the FAO Deputy Director–General. (*UN FAO*, 17 Jan 2014)

>> The WHO urged a global drive against cancers linked to lifestyle – half of which are preventable – such as alcohol abuse, sugar consumption and obesity, as it estimated that new cases could increase by 70% to nearly 25 million a year over the next 20 years. It will be hugely expensive to treat these cases, so more emphasis must be placed on prevention and early detection. Low– and middle–income countries face the biggest burden due to increasing and ageing populations. Preventative measures include price increases for alcohol and sugary drinks, and government and society should support environments that enable healthy choices, eg, diet and exercise. (*The Guardian*, 3 Feb 2014)

▶ Globally, there is an increasing pressure on water supplies, due to agriculture, population and energy demands. Climate change is causing changing rainfall patterns, as the tropics and northern areas become wetter, and the already dry arid and semi–arid areas become drier. Scarce water resources could become a flash–point for conflict at both national and local scales. The international community has tool for de–escalating national conflicts, but local conflicts are harder to deal with and may be more critical. (*The Guardian*, 9 Feb 2014)

Peace and Human Rights

>> The Walk Free Foundation's country-by-country survey on slavery found that more than 29 million people are living in slavery, and that 10 countries account for 70% of the world's slaves. India has 14 million people enslaved, China 2.9 million and Pakistan 2 million. This fits with an International Labour Organisation survey, which estimated that 21 million people are in forced labour. The hidden nature of slavery means that data are difficult to collect and analyse, and some argue that emotive terms like slavery and forced labour can confuse the issue, and may risk limiting the choices of those in desperate circumstances. However, Mr Kevin Bales, the survey lead, believes that accurate labelling and tracking of slavery is the first step towards beating it. (*The Guardian*, 17 Oct 2013)

>> The Dec 10 2013 International Human Rights Day was the 20th anniversary of the Vienna Declaration, which committed states to the promotion and protection of universal human rights and created the UN High Commissioner for Human Rights. The right to an education, the rights of children, the elimination of violence against women and the eradication of poverty were all envisaged in the declaration, but the attack on teen activist Malala Yousafzai shows the right to an education still cannot be taken for granted. Also, despite advances, Syria and the Central African Republic show that there are failings in protecting human rights. U.N. Assistant Secretary-General for Human Rights Mr Ivan Šimonović says that human rights abuses are often the first sign of conflict, and upfront action by the international community could prevent them. (Voice of America, 10 Dec 2013)

>> The UN Secretary–General Ban Ki–moon spoke out about new anti–gay legislation in Nigeria, fearing that it may fuel prejudice and violence, whilst hoping that its constitutionality can be reviewed. It introduces a wide range of offences, including 14–year jail terms for cohabiting same–sex couples. It has drawn strong opposition from the UNHCR, UNAIDS and the Global Fund, by violating many human rights and jeopardising the HIV/AIDS epidemic response. Mr Ban has repeatedly called for the total decriminalisation of homosexuality, and for countries to ensure the protection of lesbian, gay, bisexual and transgender people. (UN News, 16 Jan 2014)

>> Twenty years after a UN summit called for women to have more control over their lives, a new UN report found that today's women have fewer children, are less likely to die in childbirth, literacy is higher, and the majority of countries have gender parity for primary education. However, progress has been limited in the poorest areas, with pregnancy and childbirth being the main cause of death in women aged 15-19. Women are paid less, are more often in unsecure employment, and there are gender gaps in secondary and tertiary education. Physical and sexual violence rates remain high; eg, 1-in-3 men in the DR Congo have been sexually violent. It highlighted growing economic inequality, and the increasing concentration of the world's youngsters in poorer nations with less job prospects, and how their needs are central to their countries' development agendas. (New York Times, 12 Feb 2014)

▶ UN members met for the annual discussion on women's status, whilst facing calls to make gender equality a priority in the post–2015 framework. Progress on the female Millennium Development Goals (MDGs) has been disappointing, and countries affected by conflict and violence are furthest away from achieving them, as violence reduces women's access to health care, welfare, economic opportunities and political participation. Gender and peace are linked: peace is vital for gender equality; and gender inequality can drive violence. A stand–alone goal on gender equality and women's rights can contribute to peace, especially if it addresses attitudes and norms; and peace is vital to promote it. (*The Guardian*, 3 Mar 2014)

Science and Technology

▶ Research suggests that babies' weak immune systems, which are vulnerable to bacterial infections, may be deliberately engineered by the body. This is indicated by high levels of red blood cells expressing the protein CD71, which suppress the body's immune response. This allows beneficial microbes to colonise the baby's gut, skin, mouth and lungs. This finding could lead to new treatments for infections in newborns. Also, temporarily reducing CD71 cells may improve vaccination uptake by allowing babies to be vaccinated at birth (rather than months afterwards) – the only time when many newborns in developing countries receive medical attention. (*Nature*, 6 Nov 2013)

>> A study published in *The Lancet* costed health system strengthening and investment packages for maternal and

Resources

newborn health, child health, immunisation, family planning HIV/AIDS and malaria, and modelled their health and socio-economic returns. It recognised that the substantial reductions in maternal and child deaths in the past 20 years are insufficient to achieve MDG 4 and 5. Inadequate health systems and inefficient use of limited resources means that the leading causes of maternal and child mortality are largely preventable. It found that an additional investment of US\$ 5 per person/y in key countries would give a rate of return of up to 9 times. This represents an additional investment of US\$ 30 billion a year, ie, a 2% increase above current spending rates. It would prevent 5 million maternal deaths, 147 million child deaths and 32 million stillbirths, and produce greater economic growth via improved productivity. (*The Lancet*, 19 Nov 2013)

▶ Mr Randy Schekman, a US biologist who won the 2013 Nobel prize in physiology or medicine, claims that leading academic journals are distorting the scientific process and represent a "tyranny" that must be broken. Pressure to publish in top-tier journals encourage researchers to cut corners and focus on "trendy" research rather than doing more important work. His laboratory will no longer send research papers to *Nature, Cell* and *Science*. He criticizes toptier journals for artificially restricting the number of papers they accept, which stokes demand, and the widely–used impact factor, claiming that it distorts science results. Editors from some of top-tier journals defended their publications, eg, by saying that their mission was to serve science and scientists. (*The Guardian*, 9 Dec 2013) ▶ In 2012, over 500 potential cancer drugs were under investigation, more than five times as many as diabetes, the next biggest category. This is fuelled by increases in cancer cases as more people live longer; the rising price of cancer drugs; and the rapid expansion of scientific knowledge. All cancers arise from genetic changes within the patient's cells, and understanding these can suggest ways of attacking them with tailored drugs. Although cancer can be caused by several mutations and new mutations can develop, DNA sequencing may lead to better understanding of these mutations and the development of ever-more tailored treatments. Patients could be offered new treatments once their cancer becomes resistant to a given treatment regime. Another approach is to prime immune cells to attack cancer cells, or to boost their activity. Eventually it may be possible to combine targeted drugs with immunotherapy. (The Economist, 4 Jan 2014)

▶ Researchers studying the Plague of Justinian, an outbreak of the bubonic plague in the 6th century that killed half the world's population, have found that it was a different strain to the bubonic plague of the 14th century, which killed 50 million Europeans. This suggests that a new strain of the plague could emerge, if it follows the same pattern of separate strains of the bacterium evolving and infecting humans. However, today's antibiotics can effectively treat the bubonic plague, reducing the risk of another large–scale pandemic. (*Skynews*, 28 Jan 2014)

JOURNAL OF GLOBAL HEALTH'S NEWS TEAM:

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China's engagement in global health governance: A critical analysis of China's assistance to the health sector of Africa

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China has been providing medical assistance in various forms to Africa for 60 years, and has made notable contributions to the healthcare sector of Africa. However, China is confronted with numerous problems and challenges in offering medical aid to Africa.

In recent years, China has been getting increasingly involved in global health governance. As the largest developing country and the second largest economy in the world, China's engagement in global health governance has drawn considerable attention in the rest of the world. In this viewpoint, China's medical and health–related assistance to Africa has been used as a case study to analyse China's involvement in global health governance.

This paper will first assess China's motives and reasons for providing medical assistance to the health sector of Africa; then it will examine China's contributions and achievements in medical assistance. It will explore the major problems identified in China's medical assistance so far, and finally, it will draw conclusions based on China's only official white paper on its foreign aid. To achieve those aims, this paper will use academic articles and books, government official documents and data, working papers from non– state organizations and think tanks related to China's medical assistance to Africa.

MOTIVES FOR CHINA'S MEDICAL ASSISTANCE TO AFRICA

The history of China's official medical assistance to Africa spans over half a century. China's government dispatched medical teams to Algeria in the January of 1963, which was historically the first official Chinese medical assistance to Africa.

The motives for China to provide assistance to the health sector of Africa varied in different historical contexts. Initially, Chinese officials claimed that they offered medical assistance to Africa to improve health of African people and that their motives were primarily humanitarian. However, China's decision to provide medical assistance to Africa could also be seen as mainly driven by political considerations. Studies suggested that China's medical assistance to Africa was closely related to China's position in international geopolitical context and China's foreign policy-making [1,2]. From that point of consideration, some of the reasons for China's medical assistance to Africa may include: (i) competition with Taiwan for the seat in the United Nations, through winning support from African countries; (ii) exporting the ideology of socialist experience and proletarian internationalism; (iii) attempting to address challenges in the rapidly evolving international context, such as the sanctions from the western countries led by the US after the June Fourth Incident [2]. After the World War II and the establishment of the United Nations, Africa played an important role in the vote of international organizations, based on the rule of "one country-one vote",

which made it strategically important for China to maintain good relationships with Africa. To ensure the support from Africa, offering medical assistance was regarded as an effective method by the Chinese government.

Furthermore, economic benefits may have also been a motive for China to actively provide medical assistance to Africa in recent years, although this interpretation has been repeatedly denied by the Chinese officials. It could be argued that China's medical assistance is being used as one of the tools to pave the way for China's state–owned enterprises to win the market access in Africa. There, they could be interested in benefiting from the natural resources in countries with relatively weaker bargaining power. However, such interpretation has been denied by the State Council of China, who states that economic benefit may only be a potential outcome, rather than a motive [3].

CHINA'S CONTRIBUTIONS AND ACHIEVEMENTS IN AFRICA

The forms of China's medical assistance to Africa included: (i) dispatching medical teams, (ii) constructing health care facilities, (iii) providing medicines and medical equipment, and (iv) donating to health funds. In the past decades, China has dispatched medical teams consisting of more than 20000 medical professionals to 46 African countries and they had treated around 200 million African patients [1]. The African recipient countries and their starting year of receiving China's medical assistance are shown in **Table 1**.

 Table 1. African recipient countries and their starting year of receiving China's medical assistance

Courses	C	Courses	C
COUNTRY	START	Country	START
Algeria	1963	Gabon	1977
Zanzibar	1964	Gambia	1977
Somalia	1965	Benin	1978
Congo (Brazzaville)	1967	Zambia	1978
Mali	1968	Central African	1978
		Republic	
Tanganyika (Tanzania)	1968	Chad	1978
Mauritania	1968	Botswana	1981
Guinea	1968	Djibouti	1981
Sudan	1971	Rwanda	1982
Equatorial Guinea	1971	Uganda	1983
Sierra Leone	1973	Libya	1983
Tunisia	1973	Cape Verde	1984
Democratic Republic of	1973	Liberia	1984
Congo			
Ethiopia	1974	Zimbabwe	1985
Togo	1974	Burundi	1986
Cameroon	1975	Seychelles	1987
Senegal	1975	Comoros	1994
Madagascar	1975	Namibia	1996
Morocco	1975	Lesotho	1997
Niger	1976	Eritrea	1997
Mozambique	1976	Malawi	2008
Sao Tome and Principe	1976	Angola	2008
Guinea–Bissau	1976	Ghana	2009
Guinea-Dissau	1970	Ghana	2009

* Source: Adapted from Li [1].

China should take measures, such as formulating and developing a well-designed strategy for its comprehensive involvement in global health governance.

SOME POSSIBLE CONCERNS OVER CHINA'S MEDICAL ASSISTANCE TO AFRICA

There are some possible concerns over the content and the process of China's medical assistance to Africa, including: (i) the relatively limited financial commitment; (ii) the controversy over the effectiveness of traditional Chinese medicine (TCM); (iii) the controversy over selection criteria of the deployed medical professionals; and (iv) the assistance not being proportional to the national strength.

Considering that China is still a developing country, its total contribution to the health sector and health care–related projects of Africa could be viewed as substantial. The average annual investment in hospitals and disease control centers amounted to around US\$ 8 million and US\$ 500 000, respectively. In addition, the average annual cost of medical teams and required medicines are US\$ 14 million and US\$ 60 million, respectively [2]. Moreover, China has also made a commitment to donate US\$ 14 million before 2013 to the Global Fund, of which the major beneficiaries are African countries. Therefore, the total cost of China's medical assistance to Africa has amounted to at least US\$ 80 million in each year since 2007.

However, from the perspective of China's emerging role as the 2nd largest economy in the world, the actual amount of its medical assistance to Africa is relatively limited in comparison to other donor nations and non–governmental organizations (NGOs). The average amount of China's spending on health–related assistance to each African country that it supports is only around US\$ 1.8 million per year. As an example, **Table 2** shows the amount of support that some donor nations and NGOs commit to some of the recipient countries:

Another somewhat controversial issue is that of traditional Chinese medicine (TCM), including herbal medicine and acupuncture therapy. TCM is widely used in China's medical assistance to African countries, although its effectiveness is a matter of much debate internationally. The TCM lacks the support from double–blind randomized controlled trials, which are recognized by the modern medical science as the best way to evaluate treatments; until those trials have been conducted, the placebo effect will remain a possible explanation for much of the observed efficacy of the TCM [10].

VIEWPOINTS

 Table 2. The amount of financial support that some donor nations and international organizations provided to selected recipient countries

DONOR NATION OR ORGANIZATION	Recipient country	YEAR	Amount	Аім
France	Kenya	2010	€ 35.5 million	To strengthen the capacity of health care division
Belgium	Rwanda	2011	€ 55 million	To assist the medical and health-related needs
European Union	DRC	2010	€ 51 million	To improve its overall level of health services by sup- porting its public health development plan and im- proving its essential medicine supply system
World Bank	Southern Sudan (now the Republic of South Sudan)	2010	US\$ 63 million	To develop its health system and to improve its over- all medical and health care conditions
Global Fund to Fight AIDS, Tuberculosis and Malaria	Zambia	2012	US\$ 100 million	To scale up prevention and strengthen its health sys- tems
United States	Burundi	2012	US\$ 8.3 million	To assist the medical and health–related needs
United States	Kenya	2012	US\$ 545 million	To develop the disease control ability and to improve the health system
United States	Algeria	2012	US\$ 471 million	Same as above
United States	Tanzania	2012	US\$ 436 million	Same as above
United States	Uganda	2012	US\$ 323 million	Same as above

*Source: French Development Agency [4], Belgium Development Agency [5], European Commission [6], World Bank [7], The Global Fund [8], US Government [9].

FINDINGS AFTER ANALYZING CHINA'S FOREIGN AID DOCUMENT

Through analyzing *China's Foreign Aid*, China's first and only official document on its foreign aid so far, several findings could be proposed.

First, when providing medical assistance to Africa, China is affected by political interests. China's government claims that China would not impose any political conditions to the recipient countries. However, in fact, China suspended all the medical assistance and cooperation, and withdrew all the medical teams in the African recipient countries which respectively built formal diplomatic relationships with Taiwan during 1980s and 1990s, until those countries stopped recognized Taiwan's political status. In those cases, China's medical assistance was related to its interference of the recipient countries' own decisions on the political interactions with Taiwan.

Second, China's foreign aid has been distributed mainly through three types of financing: free grants, interest–free loans, and concessional loans. The total amount of China's financial resources committed to foreign aid has become substantial – China has pledged ¥ 256.29 billion in foreign aid by 2009; however, the amount for medical and health–related assistance seems to account for only a small part of that large budget. Only around 6% of free grants and 3% of the loans are used in the public facilities in Africa, in which the hospital, medical station and other health facilities take even smaller portion and receive fewer financial resources. Besides that, loans may not be very suitable for some African countries that are facing economic challenges and lack capacity to repay those loans.

Third, as stated in the document, the forms of China's foreign aid include: complete projects, general goods and materials, technical cooperation, human resources, development cooperation, foreign aid medical teams, emergency humanitarian assistance, overseas volunteer programs, and debt relief. Some forms, including foreign aid medical teams, general goods and materials, as well as debt relief, have evidently made contributions and played positive roles in China's medical assistance to Africa to a considerable degree; while the other forms of foreign aid did not focus on health–related issues, thus having little impact on Africa's health care.

Fourth, in terms of geographical distribution, African countries are the major beneficiary countries of China's foreign aid; while in terms of the distribution of major areas of development aid, it is evident that the assistance to the health care sector has not been the key focus of China's foreign aid, since the projects established in the health care sector are proportionally the smallest among all other areas of aid and the history of the foreign aid to the health care is shorter than that of any other area.



Photo: Courtesy of Xiangcheng Wang, personal collection

Fifthly, in terms of management of foreign aid, the State Council has nominally the leadership and management rights over China's foreign aid. However, unlike most OECD member states, which have established independent and specialized agencies for foreign aid (eg, USAID, DFID, AUSAID, NORAD and SIDA), in China, numerous ministries, departments and bureaus are authorized to partly deal with, or to be responsible for the affairs of assistance - including medical aid to Africa. There are overlapping functions between those ministries and departments and conflicts are likely to occur in the process of implementation. This reduces the efficiency of provided assistance and likely increases the cost of medical assistance. China does not have an independent and specialized agency for foreign aid, and the current foreign aid management cannot be considered effective, open, or transparent enough.

Sixthly, in terms of international cooperation, China has been trying to strengthen multilateral and regional cooperation with other aid–providers, such as the Global Fund and the Bill & Melinda Gates Foundation, to provide medical assistance to Africa since 2005.

CONCLUSION

Through examining and analyzing the existing literature on China's medical assistance to Africa, as well as conducting a critical analysis of China's only official white paper on its foreign aid, a number of key findings have been proposed. First, China's medical assistance to Africa has a history of 60 years, and has made notable contributions to the health care sector of Africa. Second, Africa is the major beneficiary region of China's foreign aid, but health care is not the most important component of China's foreign aid. Third, the forms of China's foreign aid vary and some of them indeed make contributions to Africa's health care to a different degree, while the others do not. Fourthly, the management of China's medical assistance to Africa is not effective and open enough, and China's medical aid work is not always operating coherently and properly.

Some implications could be drawn from the case study of China's medical aid to Africa for China's overall involvement in global health governance. For instance, China could attach more importance to global health governance, and could learn from the US "Global Health Initiative" and UK's "Health is Global" strategy to formulate and develop a clear, coherent and well–designed strategy or plan for its involvement in global health governance. Besides, solving domestic health care challenges would be beneficial for China's involvement in global health governance, where it could lead by example in more appropriately utilizing the limited health care resources. Moreover, China could explore opportunities to enhance international and multilateral cooperation with other actors to become more comprehensively involved in global health governance.

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Syria: What should health care professionals do?

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In Syria, inability to access healthcare has become part of daily life for millions of people. The deliberate targeting of healthcare as a weapon of war is a shocking reality.

The Syrian conflict started in March 2011 with civil unrest and has now progressed to civil war [1]. The death toll stands at more than 100000 men, women and children [2]. The UN Human Rights Council has accused both the Syrian government and the opposition of committing war crimes and crimes against humanity [3]. Within a few years, Syria has evolved from the world's second largest refugee-hosting country, to fast becoming the largest refugee-producing country [4]. UNHCR has estimated there are 9.3 million people, 1 million of these children, in need. 6.3 million Syrians are internally displaced – a number that is expected to rise if the conflict continues [4]. In these unstable conditions, health is one of the biggest concerns for these people [5].

With the conflict continuing unabated, inability to access health care is now a reality of daily life for millions of people. Syria was widely considered to have a well functioning health system before the conflict started [6]. However, with many millions of displaced, vulnerable people requiring all levels of health care, the fragile health system is under threat. This is not simply an issue of burden, but of two fundamental, catastrophic problems that must be addressed by the international community: a blocking of sufficient humanitarian aid and deliberate, direct attacks on the health care system, which are being widely used as a weapon of war [7].

Health is a right for all [8]. For this reason, hospitals, medical units and health care personnel require special protection in times of crisis. Additionally, to enable the capacity of the health system to reach adequate levels, channels of humanitarian assistance must be opened, including crossborder aid and removing control solely from the hands of the Government [9].

In Syria, the deliberate targeting of these providers is a shocking reality [10]. Numerous reports have highlighted the forcible denial of care to sick and wounded Syrian civilians [10]. According to the UN, almost two thirds of public hospitals are unable to function, and as many emergency ambulances have been rendered unable to provide services to the public. [11]. Of grave concern are reports of the deliberate targeting of health workers: in the context of wider abuses of human rights and crimes against humanity, health personnel face detention if found to be providing treatment or even simply carrying medicines [10,12].

Such destruction of the infrastructure, resources and workforce of the health system surely presents an exacerbated challenge for post-conflict rehabilitation. A growing body of evidence points to the importance of a strong health system in successful reconstruction of other sectors and the country as a whole [13]. The International Federation of Medical Students' Associations has passed policies calling for international actors to do more to protect health workers in Syria to preserve the health of Syrians.

As medical students, one development of the systematic targeting of health care is of particular concern. Two fourth year medical students from Aleppo University were arrested whilst working with a team in a field hospital treating injured demonstrators. According to Amnesty International, their bodies were later found burned and mutilated: one of the students had his hands bound and had suffered a gunshot wound to the head [14].

This threat to the depoliticised nature of humanitarian relief, or more significantly a threat to the provision of essential health care, should be something the health professions



Photo: UN photo from UNRWA archives, unrwa.org, January 2014

fight to defend against. As medical students, we have a unique mandate and responsibility to speak out against such atrocities against our colleagues in Syria, and call the UN to action over the position it has already adopted in promoting International Humanitarian Law, human rights and supporting the Declaration of Geneva [10].

In March, the International Federation of Medical Students' Associations, the IFMSA, passed two policies relevant to the Syrian conflict: the first calls for action from international actors to do more to protect health services and the health workforce in conflict situations [15]. The second calls for international actors to fulfill their funding commitments for the Syrian crisis, and supports the MSF open letter calling for more open channels of humanitarian assistance and medical aid [16]. This complements the UN Security Council Resolution 2139 in 2014 to increase humanitarian access and aid delivery in Syria. The resolution highlights the need to respect the principle of medical neutrality and to ensure, under international law, that the

wounded and sick receive medical care [17]. These policies, advocating on behalf of over 1.4 million medical students from 114 countries, represent a significant call to action for international actors to do more to preserve the health of Syrians.

Through the IFMSA, international collaboration has been initiated, which sets a precedent for other professional networks and international actors to do the same. UK medical students will work with their colleagues from Jordan, Lebanon, Kuwait and Iraq to support Syrian civilians in need. This represents the ability for health professionals from all over the world to present a united voice speaking out against human rights violations and a threat to health care. We call for the UN to turn statements into action.

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The need for ventilators in the developing world: An opportunity to improve care and save lives

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The drive to breathe is a fundamental human and biologic behavior, regulated by a complex system of checks and balances in the body. When respiratory mechanics are deregulated by injury, infection, coma, or a host of other conditions, the biologic equilibrium shifts into a state of respiratory failure. When this occurs, mechanical ventilation can be a life saving therapy. While commonplace in developed countries, critical care is at its infancy in many developing countries [1], where basic technology is often not available. Thus, while many lives are saved in developed nations through the provision of mechanical ventilation, patients in many developing nations often die from otherwise reversible causes due to lack of resources, education, and training.

In this viewpoint paper, we will explore arguments in support of and against the provision of one vital resource – mechanical ventilators – in resource–poor settings. Furthermore, we will address both the benefits and challenges in implementing a program of increased provision of mechanical ventilators. Lastly, we will provide some solutions to address potential barriers to this initiative.

BURDEN OF RESPIRATORY FAILURE IN DEVELOPING COUNTRIES: A CHALLENGE

Much of our data about the burden of respiratory failure worldwide comes primarily from developed nations. Un-

fortunately, because the disparity in quality of care within developing countries is wide [2], no reliable comparative epidemiological data of critical illness syndromes, such as acute lung injury and sepsis, are available. While respiratory failure may be fairly easy to diagnose clinically (such as hypoxia or increased work of breathing), it is a consequence of a primary disease process (ie, pneumonia) – thus, as a secondary process, collection of epidemiologic data are challenging in resource-poor settings. This results in the comparative epidemiology (between resource-intensive and resource-poor settings) of critical illness and respiratory failure being heterogeneous [3,4]. Furthermore, mortality after critical illness is related to both clinical decisions to limit intensive care and the consequences of the disease; therefore, countries with the resources to provide intensive care for patients with comorbid illnesses will have a perceived higher burden of critical illness associated with these disorders compared to countries which do not initiate treatment in the first place.

With a potentially high burden and mortality of respiratory failure in developing nations, the provision of mechanical ventilators may help save lives if implemented in a thoughtful fashion. Thus, good outcomes in this patient population may contribute to healthier patients with better future productivity and economic potential. Despite this, several barriers to implementing a greater number of ventilators exist, including perceived high cost, the need for education, and a lack of research in ventilator protocols for resource–poor settings.

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The provision of mechanical ventilators in developing nations may help save many lives, but it must be implemented in a careful and thoughtful fashion.

BENEFITS OF THE PROVISION OF VENTILATORS IN DEVELOPING COUNTRIES

As previously mentioned, the epidemiologic data regarding the burden of respiratory failure in developing countries is poor and may potentially be underrepresented due to large proportion of uncaptured data in patients in whom intensive care was never initiated in the first place due to perceived futility of treatment. Although classically thought to only benefit a small segment of patients, mechanical ventilation actually can help a wide variety of patients including patients with injury, non-communicable diseases (NCDs), and communicable diseases such as the human immunodeficiency virus (HIV) and malaria. For example, while it has been recognized that NCDs are beginning to account for a larger burden of disease in developing countries [5], decompensated NCDs (ie, heart failure exacerbations) commonly require critical care and mechanical ventilation. In the same vein, a patient with HIV infection may also decompensate from the acquisition of opportunistic infections and require mechanical ventilation.

Youth are often are disproportionately affected by critical illness and respiratory failure in the developing world; thus, a large amount of patients who have many years of contribution to society needlessly die due primarily to a lack of resources and education [6]. Furthermore, the limited data comparing critical care in Europe versus developing nations confirms that patients in developing countries tended to be younger and had an improved prior health status [7,8]; thus, the potential for recovery and productivity exists. An example of this situation is care for young patients with traumatic brain injury (TBI). In developed nations, TBI outcomes have significantly improved through careful adherence to the Brain Trauma Foundation guidelines, which emphasize appropriate respiratory care and oxygenation of the brain-injured patient [9]. In developing countries, unfortunately, many of these young patients are not given a chance for survival because of the lack of basic ventilators for respiratory support.

While mechanical ventilation can be viewed as a prolonged task in some patients, the majority of patients would only require a short course of mechanical ventilation. This is because the four most common admission criteria requiring ventilation in intensive care units in developing countries are postsurgical treatment, infectious diseases, trauma, and peripartum maternal or neonatal complications [10] – the majority of these processes are reversible over a short period of time. Therefore, the provision of a short duration of mechanical ventilation has the potential to help patients with a variety of reversible pathologies.

ARGUMENTS AGAINST THE PROVISION OF VENTILATORS IN DEVELOPING COUNTRIES

A primary argument against the provision of ventilators in developing nations is centered on the increased cost of the intervention. While tackling prevention, communicable diseases, and NCDs, the strain that providing ventilators puts on funding agencies can be substantial. Furthermore, at a very high cost per ventilator even in developed countries (average anywhere from US\$ 20000 up to US\$ 100 000), ventilators by no means are a cheap intervention. To address these issues, basic ventilators for developing countries are being developed at much lower costs. While the capabilities of these machines are not nearly as robust as more expensive machines used in developed countries, the vast majority of patients even in developed countries are ventilated for a short duration and require the "minimal settings" that most ventilators can provide. In addition, the majority evidence-based maneuvers do not require complex ventilation strategies (ie, lung-protective ventilation) [11], and can be provided with a basic ventilator. Lastly, as mentioned above, funding priorities can continue to be met, as ventilators will improve care for patients with diseases under well-funded projects (ie, decompensated HIV, malaria, NCDs). Even if funding for basic ventilators is provided, it will be a disproportionately small amount of funding as compared to other disease states such as HIV [12].

While we have explored the cost to society and funding agencies as a barrier to implementing mechanical ventilation in resource-poor settings, a likely important reason for ceasing (or, not even starting) intensive care in developing countries is the family's inability to keep up with the cost of caring for the patient - in the extreme case, sometimes driving families into poverty. On the other hand, if cost to the family was not an issue (as is the case in many developed countries), the challenge may shift to clinical ethics; because of religious or cultural beliefs coupled with a misunderstanding of treatment effectiveness (a situation that is often faced in developed countries as well), patients receive mechanical ventilation long after it will be of any benefit. Therefore, an ethical framework would be necessary to advise both doctors and patients of possible decisions on the withdrawal of care or transition to "comfort" care. Furthermore, if demand outSeveral barriers need to be overcome in order to implement mechanical ventilation effectively and successfully in developing countries.

strips the supply of ventilators, decision rules will need to be put into place to ethically select which patients with benefit the most from the therapy.

Aside from cost, another compelling argument against the provision of ventilators in resource–poor settings is the inadequacy of current systems to appropriately care for patients on ventilators and the ventilators themselves [13]. The initial of care for the patient with respiratory failure (ie, from trauma) is often in the field, and appropriate emergency medical services (EMS) training must involve appropriate initial care and triage of these patients.

It must be understood that mechanical ventilation is a complex task more than just merely "turning on" the machine. The act of putting a patient on mechanical ventilation requires the provision of an endotracheal tube (or tightly–fitting non–invasive face mask), making adjustments to the machine to meet patient needs, responding to ventilator crises, adequate sedation of the patient, and appropriate patient weaning and eventual liberation of the patient from mechanical ventilation. Second, ventilators can be vulnerable machines and require appropriate maintenance. Third, ventilators require both electricity and compressed oxygen, both potentially scarce resources in developing countries; in order to fulfill the ethic principle of equity, basic oxygen and electricity must be available throughout a region before considering the institution of mechanical ventilation. Thus,



Photo: Courtesy of Alasdair Campbell, personal collection

it is apparent that beyond simply providing ventilators to resource–poor settings, appropriate systems must be put into place to address issues of both care of the ventilated patient and care of the ventilator itself; the opportunity cost of this may involve shifting resources from other public health priorities, thus system changes need to be implemented in a thoughtful, evidence–based manner.

OVERCOMING BARRIERS TO THE PROVISION OF MECHANICAL VENTILATION

Reaching to goal of delivering high quality respiratory care is lofty, but very possible with a systematic approach to funding, education, and research. First and foremost, educational initiatives would be needed to address several issues; not only would physicians and nurses need training on appropriate care of the ventilated patient, but staff would also need to be trained on the care and maintenance of these machines. Second, systems would need to be in place to create protocols for complex processes to provide consistent evidence-based care to patients - checklists have been proven very successful in this regard. Third, several protocols from developed countries will likely need to be modified to best meet the needs and resources of developing countries [14]. Fourth, government systems would need to be in place to assure consistent power (ie, electricity) and oxygen for the machines. Fifth, a triage system would likely be needed to "regionalize" care for sick and complex patients who require more advanced therapies beyond basic ventilator management. Sixth, from a donor and funding perspective, greater education needs to be provided to donors that critical care and mechanical ventilation can be cost-effective, and that most evidence-based criti-

> cal care interventions tend to be inexpensive [1]. Furthermore, the economic implications and advantages of decreasing mortality in young populations would need to be stressed. Lastly, research should be performed in resource–poor settings to focus on needs assessment, education, implementation, and cost–effectiveness. While the necessary steps above seem complex, we have already proven that the global health community can tackle complex obstacles – the successful implementation of HIV care (one of the most complex diseases known to modern society) in some of the world's most destitute regions is proof of this.

CONCLUSION

The first formal use of ventilators in modern medicine is reported to have started by Dr Bjørn

VIEWPOINTS

Ibsen in Copenhagen in 1953, whose use of mechanical ventilation helped to save scores of lives of patients with polio who were dying of respiratory failure, reducing mortality from 87% to 25% [15]. Over the subsequent decades, the use of mechanical ventilation in developed countries has been refined, and now is one of the defining interventions of critical care medicine in the developed world. Through extensive experience, creation of effective systems, protocol development, and research, mechanical ventilation has become a life–saving intervention. Similar to Copenhagen in 1953, in present–day resource–poor settings, the practice of intensive care is likewise in an early stage of development, and the provision of ventilators may have the potential to have a positive impact on reducing mortality from a myriad of etiologies. As with any new intervention, providing ventilators to developing nations comes with not only benefits, but also a host of new challenges to overcome. The key to moving forward is to help funding agencies understand the benefits, while putting together a detailed plan (as outlined above) to address the limitations. With this understanding, the provision of mechanical ventilators to developing countries has the unique potential to help make a dramatic improvement in the care of the world's most vulnerable patients.

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Redefining global health priorities: Improving cancer care in developing settings

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Every year, more than 10 million people are diagnosed with cancer. Over half of them live in the developing world, where the cancer incidence rate has reached pandemic proportions. In 2008 there were upward of 12.4 million estimated new cases of cancer, with approximately two-thirds of the estimated 7.6 million cancer deaths occurring in low-and middle-income countries [1]. Although low- and middle-income countries bear the majority of the disease burden, their health systems are inadequately prepared to address the challenge of care. Since cancer kills more people worldwide than HIV/AIDS, tuberculosis, and malaria combined, it needs to be a global health priority.

Low– and middle–income countries bear the greatest burden of new cancer cases as well as deaths, amid an ever– increasing total number of affected individuals worldwide. In 2012 an estimated 14 million new cases were reported, with this figure anticipated to rise to 22 million over the next twenty years [1]. Significantly, more than 60% of the world's total cancer cases occur in Africa, Asia, Central America, and South America, while greater than 70% of the world's cancer deaths come from these same regions [2]. By 2030 the developing world is expected to account for 70% of newly reported cancer cases. What is more, survival rates are meager in poor countries and on the rise in wealthy ones [3]. For a wide range of cancers, an individual's likelihood of surviving is closely and positively related to country income (**Figure 1 and 2**).

Part of the reason why low- and middle-income countries lag behind wealthy nations in cancer survival rates is a lack

Every year, more than 10 million people are diagnosed with cancer. Over half of them live in the developing world, where the cancer incidence rate has reached pandemic proportions.

of awareness, prevention, and early detection, as well as inaccessibility of new and more effective treatments that have been developed in recent decades and made available to many in the first world. Greater than 30% of cancer–related deaths in the developing world are estimated to be preventable [2]. Thus, in the case of low– and middle–income countries, the demand for cancer prevention and treatment services is far from being met. With burgeoning survival rates among those suffering from AIDS and other diseases in low– and middle–income countries the prevalence of cancer will only increase, thereby resulting in an even greater need for cancer services in these areas.

While significant attention and financial support has resulted in expanded access to treatment for AIDS and other infectious diseases over the past decade, cancer is a concern that remains relegated to the periphery of the global health community. Despite its prevalence throughout the developing world cancer is conspicuously absent from central global health programs, including the United Nations Millennium Development Goals [4].

Cancer is a leading cause of mortality in low– and middle– income countries, equaling over five million annually. Disproportionate access to prevention and treatment, in addi-

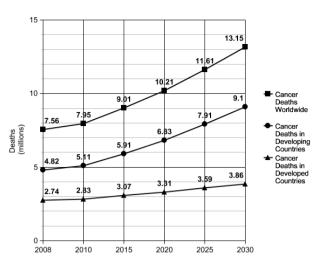


Figure 1. Countries in the developing world bear the greatest burden of new cancer cases as well as deaths. By 2030, the developing world is expected to account for 70% of newly reported cancer cases [3].

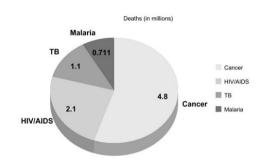


Figure 2. Deaths due to cancer, HIV/AIDS, tuberculosis (TB), and malaria in the developing world. Cancer kills more people worldwide than HIV/AIDS, TB, and malaria combined [3].



Photo: Aliasgher Saajan, Healthnovations International

tion to an ageing and growing population and decreasing mortality rates resulting from infectious diseases, will cause new cancer cases and cancer mortality to continue to rise in coming years. The global health community must take decisive action to bridge the cancer divide between wealthy and poor nations. Such action should take the form of increased access to drugs for treatment and palliation, expanded coverage for preventive and diagnostic services, as well as development and implementation of innovative health care delivery options to support rapid scale–up, while integrating access to patients in resource–poor regions through national health insurance systems.

STRATEGIC APPROACH FOR CANCER CARE IN DEVELOPING SETTINGS

Provision of widespread and comprehensive cancer care is subject to criticisms that resemble those aimed at similar calls for control of HIV and MDR tuberculosis in previous years. In the case of HIV, some argued that antiretroviral treatment was too expensive to administer widely in the developing world, and that prevention, palliation, and less expensive treatments were the only justifiable and feasible options available [5]. In the cases of HIV and MDR tuberculosis, initially–expensive treatment became widely available when innovative treatment models and new investments were developed and implemented [6]. As a result of these efforts the number of HIV infected individuals receiving antiretroviral treatment increased more than 10-fold from 2003 to 2008, numbering, at the time, over 4 million [7].

Improving access to antiretroviral treatments for HIV patients models the fact that effective treatment for wide-

> spread diseases can be administered in low– and middle–income countries. However, as with AIDS, prevention is as necessary as treatment. Neglecting prevention results in unaffordable and overwhelming treatment demands just as neglect of care results in unnecessary death and suffering. An approach that integrates prevention and treatment is necessary in any effort to control cancer in the developing world.

PROMISING INTERVENTIONS FOR CANCER CARE IN RESOURCE– POOR SETTINGS

While direct access to oncological surgery facilities will remain a hurdle in low– and middle–income countries, existing initiatives have shown that health systems can be implemented in a cost–effective manner [8,9]. The key to these systems' success lies in establishing functional primary care health infrastructures, particularly for cancers that are responsive to prevention and early detection efforts, as well as cost–effective generic drugs. Opportunities to educate, diagnose, and provide surgery, therapeutics, and palliative care to cancer patients in low- and middleincome countries should be identified and exploited. Moreover, an increase in the number of community health professionals and facilities, as well as access to prevention and early detection, will represent substantial progress in the local health infrastructure which will ultimately translate into improved health outcomes. While a robust health infrastructure has a direct impact on health outcomes, it also works to alleviate economic hardship through job creation in local economies resulting from technology transfer, an emergent service industry based on mobilization and utilization of health care professionals, and a host of other task-based positions that will emerge as a direct result of a functioning infrastructure [10]. Such an infrastructure, therefore, will serve to not only decrease mortality and morbidity due to the disease itself, but also effectively lessen the poverty-related hardship that can lead to disease faced, in particular, by marginalized communities.

Along with building the local health infrastructure, the potential of novel therapeutics needs to be exploited in developing settings. Nanotechnology is a multidisciplinary field, which includes a vast and diverse array of therapeutics derived from chemistry, physics, engineering, and biomedicine. Nanotechnology involves the manipulation of properties and structures at the nanoscale. Nanotechnology holds the promise of providing many significant benefits in medicine. For instance, Nanotechnology is being used for applications ranging from more effect drug delivery systems to highly sensitive pathogen detection platforms. To that end, the US National Institutes of Health has established the National Cancer Institute Alliance for Nanotechnology in Cancer in order to dedicate concerted efforts and resources for the development of cancer diagnostics and therapeutics. Such applications of nanotechnology in the diagnosis and treatment of disease are collectively known as "nanomedicine" [11].

Conventional medicine is largely inaccessible to patients in the developing world because of its dependence on technology, laboratory facilities, and/or highly-trained medical professionals. Conversely, nanomedicine, based predominantly on prevention and early management of disease, bypasses the need for scarcely-available, expensive laboratory equipment and medical expertise. Additionally, nanotherapeutics are fabricated in a highly-specific manner at a nanoscale level using bottom-up molecular manufacturing methods, which makes these nanomedicine drugs easier to manufacture, distribute, and subsequently administer to patients, all of which translate into improved health outcomes in resource-limited settings [12]. Currently, nanotechnology–based medicine is considered not only a significantly promising path to accurate cancer diagnosis and effective treatment, but also a plausible way to prevent and manage several chronic diseases. As nanomedicine evolves and becomes increasingly mainstream in clinical care, it is imperative to recognize its promise for combating the disproportionately high disease burden in the developing world. Applications of nanomedicine such as point–of–care diagnosis and effective nanoparticle– based drugs and vaccinations have the potential to revolutionize global health.

Part of the reason why low- and middle-income countries lag behind wealthy nations in cancer survival rates is a lack of awareness, prevention, and early detection, as well as inaccessibility of new and more effective treatments that have been developed in recent decades and made available to many in the first world.

SCALING–UP CANCER CARE IN THE DEVELOPING WORLD

We know that cancer is among the most pressing, and growing, global health challenges [13]. However, as the need for access to cancer care in low– and middle–income countries increases, the amount of resources devoted to the developing world remains stagnant. Indeed, a mere 5% of all resources devoted to cancer care globally are allotted to the developing world [14]. Considering the continually– increasing number of individuals worldwide who will be diagnosed with cancer, lack of funding for care (**Figure 3**)

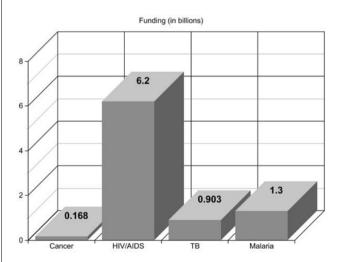


Figure 3. Funding (in US\$) allocated to combat cancer, HIV/ AIDS, tuberculosis (TB), and malaria in the developing world. Funding for prevention and treatment of cancer amounts to approximately 2% of what is put towards other diseases [13].

VIEWPOINTS

Along with building the local health infrastructure, the potential of novel therapeutics needs to be exploited in developing settings.

coupled with limited access to oncology physicians and treatment centers in low– and middle–income countries forecasts a global health disaster–in–waiting.

Many who have been diagnosed with cancer live and die in rural, resource–poor settings. Given the rising number of cancer cases worldwide, and the knowledge that a wide range of cost–effective measures exist to meet the global challenge of cancer, rapid and comprehensive scale–up of education, prevention, treatment, and palliation should be undertaken immediately. By implementing education, prevention, and affordable treatment now, while simultaneously taking expeditious steps toward developing innovative funding strategies for currently cost–restrictive care, global availability of cancer care can become a reality unbounded by income level or location.

CONCLUSIONS

In light of evidence that cancer prevention, diagnosis, treatment, and palliation is feasible across low— and middle—income countries, we call for the global health community to renew its efforts to make cancer drugs and other treatments affordable and accessible to all. We propose that cancer care and control be made available worldwide without delay, with particular attention paid to treating cancers that can be prevented or cured, and palliating those that cannot. We propose immediate implementation of the following: First, define and create new infrastructure, train health professionals and paraprofessionals, and harness technology especially telecommunications – to overcome geographic constraints, while identifying strategies that effectively alleviate the burden of cancer and expand health services in developing countries. Second, design and implement regional and global pricing and procurement standards to offer collective negotiation opportunities with an aim to reduce prices for essential services, drugs, and vaccines. Third, identify and implement innovative financing mechanisms to expand financial resources available for prevention, treatment, and palliation of cancer in low- and middle-income countries. Fourth, develop methods to support the creation of national policies surrounding cancer treatment to facilitate the implementation of the actions listed above.

Recalibrating global cancer care and control efforts could be transformative, but this kind of change will require a steadfast commitment to building integrated health infrastructures in the most marginalized settings, developing novel therapeutics specifically for resource-limited settings, and facilitating coordination between international organizations, bilateral donors, national research funding bodies, nongovernmental agencies, governments, and local regional, and global civil society organizations in order to secure funding, maximize efficiency of implementation, and ultimately improve health outcomes. Extension of cancer prevention, diagnosis, and treatment to those suffering or at risk is an urgent global health concern. Bold research, financing, and implementation strategies are essential to fill the cancer care and control void between low-, middle-, and high-income countries, and should be undertaken in earnest without delay.

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Household malaria knowledge and its association with bednet ownership in settings without large–scale distribution programs: Evidence from rural Madagascar

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Paul J. Krezanoski Department of Medicine Massachusetts General Hospital 55 Fruit Street Boston MA 02114, USA pkrezanoski@partners.org **Background** Insecticide–treated bednets are effective at preventing malaria. This study focuses on household–level factors that are associated with bednet ownership in a rural area of Madagascar which had not been a recipient of large–scale ITN distribution.

Methods Data were gathered on individual and household characteristics, malaria knowledge, household assets and bednet ownership. Principal components analysis was used to construct both a wealth index based on household assets and a malaria knowledge index based on responses to questions about malaria. Bivariate and multivariate regressions were used to determine predictors of household bednet ownership and malaria knowledge.

Results Forty–seven of 560 households (8.4%) owned a bednet. In multivariate analysis, higher level of malaria knowledge among household members was the only variable significantly associated with bednet ownership (odds ratio 3.72, P<0.001). Among respondents, predictors of higher malaria knowledge included higher education levels, female sex and reporting fever as the most frequent or dangerous illness in the community. Household wealth was not a significant predictor of bednet ownership or respondent malaria knowledge.

Conclusion In this setting of limited supply of affordable bednets, malaria knowledge was associated with an increased probability of household bednet ownership. Further studies should determine how such malaria knowledge evolves and if malaria–specific education programs could help overcome the barriers to bednet ownership among at–risk households living outside the reach of large–scale bednet distribution programs.

Malaria is a leading cause of mortality and morbidity in sub–Saharan Africa, accounting for over one million deaths each year and 600 000–800 000 deaths among children less than five years of age [1,2]. Malaria is a significant health problem in Madagascar, representing a significant burden for the health system. Malaria–related illness makes up 16% of all outpatient visits and is the leading cause of child mortality, killing nearly 20000 children under five years of age every year [3].

Insecticide–treated bednets (ITNs) are one of the most effective tools for preventing malaria [4,5]. ITNs are estimated to be as cost–effective as the measles vaccination [6] and ITN ownership is associated with an 18%–23% decrease in child mortality in sub–Saharan African households [7].

According to the World Health Organization (WHO), large–scale distribution programs in sub–Saharan Africa have improved access to ITNs in recent years, with the percentage of households owning at least one ITN rising from an average of 3% in 2000 to 53% in 2012 [8]. Nevertheless, ITN coverage continues to lag behind the Roll Back Malaria Partnership goal of 80% ITN coverage of under five-year-old children by 2010. Indeed, in Madagascar, only 46% percent of children under five were sleeping under ITNs based on 2006–2010 estimates [9].

Understanding what factors predict household ownership and use of nets is important for improving policies and programs to increase ITN coverage. Most recent studies of the predictors of bednet ownership and use have taken place in the setting of large distribution campaigns. Fewer studies have looked at the predictors of bednet ownership and use outside of subsidized distribution programs or outside of controlled trials [10–13]. This is of particular interest because households that do not contain members who are targeted for subsidized distribution programs, such as children under 5 years or pregnant women, continue to encounter a relatively scarce supply of quality and affordable ITNs [14,15].

We undertook this study in order to identify household– level factors that are associated with bednet ownership in a rural area of Madagascar. We were interested in why some households seek out bednets even when they are not provided for free or as part of large–scale programs. We also investigated predictors of high levels of malaria knowledge to further our understanding of the generic origins of household demand for ITNs.

METHODS

This study is a secondary analysis of baseline data from a previously reported cluster randomized-controlled trial. That study was a comparison of the effects of householdlevel incentives on bednet ownership and use in rural villages in the Ambalavao district of Madagascar. Full details of the study design have been published previously [16]. In brief, 20 villages within 5 km of Ambalavao town were included and all households within each village were eligible for participation. The entire country of Madagascar is considered to be at risk for malaria. The Ambalavao district is located in the southern highlands in the Haute Matsiatra region and experiences stable year-round malaria transmission, with the majority of cases occurring during the rainy season from January to April. The study began in 2007, with no recent free nor subsidized bednet distribution programs in the area. Bednets were available only at specialized pharmacies and private shops in Ambalavao town. Thus, this study was implemented in a context similar to many other sub-Saharan African countries where bednets are available in scarce supply and/or with significant cost barriers to ownership.

A baseline survey was performed to collect demographic information about the households. The survey respondent was preferably the head of household if available at the time of the home visit, otherwise the respondent was another adult in the household. Information recorded included the respondent's relation to the head of household, age, gender, education level, perceptions of malaria risk, malaria knowledge, and household assets, fuel and water sources, self– reported bednet ownership, visual confirmation of whether a bednet was mounted above a sleeping surface in the household, recent fevers and fever–related deaths in the household. The Malagasy term *tazo moka*, literally "fever from mosquitoes," was used in all questions about malaria, unless otherwise stated.

The primary outcome of interest was household bednet ownership at the time of the baseline survey. A secondary outcome was the survey respondent's malaria knowledge as defined by the malaria knowledge index detailed below. Bednet ownership was based on self–reported ownership by the survey respondent; ownership was not verified by the surveyor. Bednet use was not used as an outcome because of the inadequate variation for in–depth analysis due to the small sample of households that owned bednets.

The following variables were examined as potential predictors of bednet ownership: the age, gender and years of formal schooling of the household head, number of household members, occurrence of a febrile illness within the household in the last month, number of children under five years of age, number of pregnant women, use of an open water source, distance to water source, household wealth quintile (detailed below), the survey respondent's report of fever as the most dangerous or most common illness in the community and the respondent's malaria knowledge index (detailed below).

A wealth index was constructed by applying principal components analysis to twenty-seven binary variables representing household assets including goods, livestock, and housing characteristics such as roof and flooring materials, and number of rooms and beds [17]. The first principal component was extracted and designated as the wealth index. Only the number of rooms and beds in the household were adjusted for the number of household inhabitants [18]. Per convention, the wealth index was categorized into quintiles for analysis.

Similar to the wealth index described above, we constructed a malaria knowledge index by applying principal components analysis to the responses to twelve questions about the mechanism of transmission of malaria, malaria symptoms, knowledge of greater severity of malaria in children and pregnant women, knowledge of malaria seasons and means of protection against malaria. The first principal component was extracted and designated as the malaria knowledge index. Given the distribution of the malaria knowledge scores (see below), participants were categorized into 2 groups representing low and high levels of malaria knowledge.

All analyses were performed using Stata 10 (StataCorp, College Station, Tex., USA). First, we used bivariate logistic regression models for each independent variable with household bednet ownership as the dependent variable. Then, we conducted a multivariate logistic regression including all independent variables which had a significant predictive value with a P < 0.25 in the bivariate analysis [19]. The steps above for the bivariate and multivariate regressions were repeated with an analysis looking at the determinants of malaria knowledge, with the malaria knowledge index as a dependent variable and independent variables capturing household and respondent characteristics. Finally, since the survey respondents were not always heads of households or other "decision makers" in the household, we performed confirmatory sub-analyses restricting the sample to only survey respondents who were 1) heads of households, 2) wives of heads of households or 3) household decision makers, defined as either heads of households or wives of heads of households.

As noted in the original study [16], "Ethical clearance for this study was provided by the Boston University Medical Campus Institutional Review Board. Additional administrative approval was provided by the mayor of the town of Ambalavao, responsible for the villages in the district, and the Medicin Inspecteur of the Ambalavao health district, the local official in charge of all health–related activities in the district. Additionally, the chiefs of each village gave their approval for the study to take place in their village. Study participants provided verbal consent at the time of the surveys and coupons for the free ITNs werse provided to all households in the study villages irrespective of whether or not they consented to participate in the study." In addition, the specific analysis described in this manuscript was reviewed and approved by the Partners Human Research Committee.

RESULTS

Data were collected from 560 households containing 2881 individuals in 20 villages (Table 1). A majority of households (n=346, 62%) had at least one child under five years

Table 1. Village, household and individual respondent characteristics

Variable	
Village characteristics (n=20 villages)	
Households per village (mean ± SD)	28.0±14.7 (range 9–61)
Households using open water source (n [%])	371 (66.3%)
Village distance to open water source (meters) (mean \pm SD)	8.9±8.6 (range 0–40)
Household characteristics (n = 560 households)	
Total individuals in study households	2881
Members per household (mean \pm SD)	5.1 ± 2.7 (range 1–20)
Female head of household (n [%])	150 (26.8%)
Men per household (mean \pm SD)	2.4 ± 1.7
Women per household (mean ± SD)	2.7 ± 1.7
Children under 5 per household (mean \pm SD)	0.94 ± 0.90 (range 0–5
Households with at least one child under 5 (n [%])	346 (61.8%)
Pregnant women per household (mean \pm SD)	0.05 ± 0.23 (range:0-2)
Households with at least one pregnant woman (n [%])	34 (5.2%)
Households reporting member with fever in last month (n [%])	186 (33.2%)
Households reporting death last year due to fever (n [%])	1 (0.2%)
Selected household asset characteristics (n=560 households)	1 (0.2 /0)
Thatch roofing (n, %)	440 (78.6%)
Dirt flooring (n, %)	504 (90.0%)
Dirt/mud walls (n, %)	555 (99.1%)
Charcoal for main cooking fuel (n, %)	534 (95.4%)
Number of cattle (mean \pm SD)	1.4 ± 2.8 (range 0–27)
Number of chickens (mean \pm SD)	3.7 ± 9.2 (range 0–27)
Own at least one (n, %)	5.7 ± 9.2 (range 0–100)
radio	424 (75.7%)
bicycle	149 (26.6%)
cellphone	
cattle drawn cart	21 (3.8%) 40 (7.1%)
motorcycle/automobile	0 (0%)
Individual respondent characteristics (n = 560 individuals)	0 (0%)
Gender – female (n, %)	452 (80.7%)
Age (mean \pm SD)	
Married $(n, \%)$	38.7 ± 16.3 (range 14–96)
Relation to head of household (n, %):	368 (65.7%)
wife	2EA(AEA0/)
	254 (45.4%)
household head	250 (44.6%)
child	44 (7.9%)
other (parent, sibling, grandchild)	12(2.1%)
Number of children (mean \pm SD)	3.5 ± 2.8 (range 0–15)
Years of education (mean \pm SD)	4.9±2.9
Number of years in school (n, %)	
0	69 (12.3%)
1-4	183 (32.7%)
5-8	224 (40.0%)
9–12+	84 (15.0%)
Self–reported literacy (n, %)	487 (87.0%)

old and 29 (5.2%) had a pregnant woman residing there. Thirty–three percent of households (186) reported having at least one household member with a fever in the preceding month. Among the survey respondents, 254 (45%) were the heads of their households and 250 (45%) were the wives of the household heads. Most respondents were female (452, 81%) and had an average age of 39 years. Respondents averaged approximately 5 years of education and 69 (12%) respondents had never attended school.

Eighty–two percent of respondents (n = 489) identified fever as the most common illness in their communities and 294 respondents (53%) reported fever as the most dangerous illness (Table 2). Seventy–three percent identified mosquitoes as the mechanism for acquiring fevers and 44% listed bednets and avoidance of mosquitoes as a means of protection against malaria. Most respondents recognized

 Table 2. Beliefs and perceptions of malaria (n = 560)

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Perception/belief	No. (%)
Perceptions of malaria:	
Fever as most frequent illness in village	489 (82.3)
Fever as most dangerous illness in village	294 (52.5)
Mechanism of acquiring malaria:	
Mosquitoes	407 (72.7)
Getting chilled/overheated	48 (8.6)
Poor hygiene/unkempt household	45 (8.1)
Bad food/water	15 (2.6)
Unripe fruits	13 (2.4)
Other (fatigue, rats, etc)	9 (1.6)
Unsure	23 (3.9)
Symptoms of malaria:	
Chills/rigors	249 (44.4)
Headache	228(40.8)
Listless	29 (5.1)
Vomiting	16 (2.8)
Agitation	9 (1.6)
Seizures/shaking	2 (0.3)
Other (coughing, trouble breathing, etc)	15 (2.9)
Unsure	12 (2.1)
Protection against malaria:	
Use bednet/avoid mosquito bites	246 (44.0)
Use natural medicines	108 (19.3)
Keep household clean	85 (15.1)
Take medications	62 (11.1)
Visit hospital/doctor	13 (2.3)
Avoid unripe fruits	12 (2.1)
Stay warm	9 (1.6)
Other (boil water, get vaccinated, etc)	11 (2.1)
Unsure	14 (2.6)
Severity pairings:	
Malaria is more of a risk in	
men	52 (9.3)
women	(321 57.3)
same	187 (33.4)
Malaria is more of a risk in	
adult	6 (1.1)
child	376 (67.1)
same	178 (31.8)
Malaria is more of a risk in	
non-pregnant women	5 (0.9)
pregnant woman	385 (68.8)
same	170 (30.4)
Frequency pairings:	
Malaria is most common in	
wet season	452 (80.7)
dry season	100 (17.9)
same	8 (1.4)
Malaria is most common in	
cold season	489 (87.3)
warm season	62 (11.1)
	9 (1.6)

that malaria is more severe in children (67%) and pregnant women (69%). Eighty–one percent of respondents reported that malaria is most common when the weather is wet and 87% thought malaria was most common when it is cold.

The wealth index had a normal distribution with a rightward skew (Figure 1), while the distribution of malaria knowledge in this population, as defined by our knowledge index, showed a bimodal pattern (Figure 2).

At baseline, 47 households (8.4%) owned a bednet and 34 (6.1%) had it mounted over a sleeping area as observed by the surveyor (**Table 3**). Most households had paid for their bednet, with 13 paying 1000 Ar (Malagasy Ariary; US\$ 0.63), 27 households paying 3000 Ar (US\$ 1.90) and the source was unavailable for seven bednets. Overall, 25 of 524 (4.8%) children under 5 years of age were reported to have slept under a bednet the night before. Among households in which a bednet was observed to be mounted over a sleeping area, 25 out of 33 (76%) of children under 5 were reported to have slept under the bednet the previous night. One of 30 households (3.3%) with pregnant women

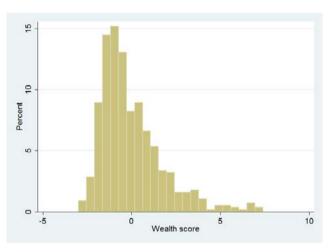


Figure 1. Distribution of wealth index for principal component analysis of household assets.

Table 3. Household (n = 560) bednet ownership characteristics

Characteristics	No (%)
Report net ownership	47 (8.4)
Observed net mounted	34 (6.1)
Number of nets owned:	
one	44/47 (93.6)
two	3/47 (6.4)
Age of net (years):	
≤1	23/47 (27.7)
2–4	11/47 (23.4)
≥5	5/47 (10.6)
unsure	8/47 (17.0)
Reports child under 5 y using a net the night before	25/524 (4.8)
if household owns bednet	25/47 (53.2)
if bednet is mounted	25/33 (75.8)
Reports pregnant women using a net the night before	1/30 (3.3)
if household owns bednet	1/1 (100.0)
if bednet is mounted	1/1 (100.0)

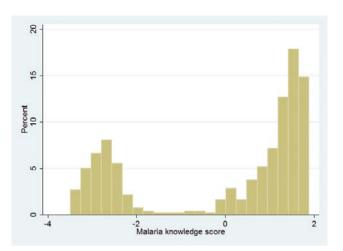


Figure 2. Distribution of knowledge index for principal component analysis of respondent malaria knowledge.

reported that the pregnant woman slept under a bednet the night before.

The results from the bivariate analysis show that malaria knowledge, household wealth, household size, households reporting a fever during the previous month were all associated with bednet ownership (Table 4). In the multivariate analysis, a higher level of malaria knowledge was the only variable significantly associated with household bednet ownership (OR 3.72, 95% confidence interval (CI) 1.83–7.55%, P<0.001). Evaluated at the mean of the other covariates, a household with a survey respondent with less malaria knowledge had a 3.4% likelihood of owning a bednet (95% CI 1.9–6.2%) vs 11.6% (95% CI: 8.2%–16.1%) in households with respondents with higher levels of malaria knowledge. A similar strong association between malaria knowledge and bednet ownership was the only

significant finding in multiple sub–analyses of the sample, including survey respondents who were heads of house-holds only, wives of heads of households only and house-hold "decision makers", ie, heads of households or wives of heads of households (Online Supplementary Document). Restricting the sample to respondents who were heads of households only showed an even stronger association with bednet ownership (OR 5.82, 95% CI 1.09–30.84, P=0.038).

Significant independent correlates with a higher malaria knowledge index score included the respondent's perception that malaria was the most frequent or most dangerous illness in the community, female gender, being married, education level of the respondent and whether the household reported a fever in the previous month (Table 5). In the multivariate analysis, high levels of malaria knowledge were correlated with both the respondent's education level (OR 1.11, 95% CI 1.04–1.18, P=0.001) and the respondent being a female (OR 1.77, 95% CI 1.12–2.79, P=0.015). Additionally, reporting a fever as the most frequent (OR 2.34, 95% CI 1.00–5.47, P=0.049) or most dangerous illness in the community (OR 1.87, 95% CI 1.09–3.22, P=0.023) was associated with higher respondent malaria knowledge. However, fevers reported in the household in the last month were not predictive of higher malaria knowledge.

DISCUSSION

In this cross–sectional analysis of data from 560 households in rural Madagascar without access to ITNs as part of a large–scale ITN distribution program, malaria knowledge was independently and highly associated with bednet ownership. Our multivariate model demonstrated that

Table 4. Significant correlates of household bednet ownership (n = 560 observations)

Variable	B ivariate analysis		Multivariate analysis	
	OR (95% CI)		OR (95% CI)	
Head of household (HH) characteristics:*				
Age of HH	1.01 (0.99–1.04)	0.352	_	-
Gender of HH	0.66 (0.21-2.11)	0.483	-	-
Education level of HH	1.08 (0.90–1.30)	0.413	_	-
Household characteristics:				
Number of HH members	1.12 (1.02–1.24)	0.019	1.09 (0.98–1.22)	0.125
Reported fever in last month	1.70 (0.93–3.12)	0.084	1.49 (0.79–2.79)	0.217
Number of children under 5 years	1.12 (0.81–1.54)	0.497	—	_
Number of pregnant women	1.21 (0.37-3.96)	0.753	-	-
Open water source	0.99 (0.52–1.85)	0.965	-	-
Distance to water source (minutes walk)	1.00 (0.97–1.03)	0.976	-	-
Wealth index (quintile relative to lowest wealth quintile):				
Second	0.95 (0.33-2.73)	0.930	0.73 (0.25–2.15)	0.562
Third	0.64 (0.20-2.01)	0.441	0.53 (0.16–1.71)	0.284
Fourth	1.34 (0.51–3.52)	0.558	1.00 (0.36–2.79)	0.999
Fifth	2.44 (1.01-5.90)	0.048	1.84 (0.69-4.95)	0.226
Respondent perception/knowledge of malaria:				
Reports fever most frequent illness in village	0.68 (0.31–1.53)	0.352	-	-
Reports fever most dangerous illness in village	1.24 (0.68–2.27)	0.479	-	-
Malaria knowledge index	3.61 (1.80-7.24)	< 0.001	3.72 (1.83–7.55)	< 0.001

CI – confidence interval

*n=256 because of missing variables.

Table 5. Correlates of higher levels of malaria knowledge (n=560 observations)

	B ivariate analy	/SIS	Multivariate anai	LYSIS
Variable	OR (95% CI)	P value	OR (95% CI)	P value
Respondent characteristics and perceptions:				
Age of respondent	1.00 (0.99–1.01)	0.560	_	-
Female gender	2.02 (1.31-3.12)	0.001	1.77 (1.12–2.79)	0.015
Marriage status	1.29 (0.91–1.83)	0.155	1.21 (0.83–1.75)	0.315
Number of children	1.00 (0.95–1.06)	0.916	_	_
Pregnancy status	1.21 (0.51–2.85)	0.430	_	-
Education level	1.16 (1.05–1.18)	< 0.001	1.11 (1.04–1.18)	0.001
Reports fever most common illness	2.90 (1.68-5.00)	< 0.001	2.38 (1.35–4.19)	0.003
Reports fever most dangerous illness	2.12 (1.52-2.98)	< 0.001	1.81 (1.27–2.59)	0.001
Household characteristics:				
Number of inhabitants	0.99 (0.93–1.05)	0.673		
Reported fever in last month	1.47 (1.03–2.10)	0.032	1.27 (0.87–1.86)	0.210
Number of children under 5 y	1.11 (0.92–1.34)	0.261	_	
Number of pregnant women	1.30 (0.64–2.67)	0.470	_	
Open water source	0.84 (0.59–1.19)	0.326	_	
Distance to water source	1.00 (0.98–1.02)	0.654	_	
Wealth index in greatest 20%	0.87 (0.51–1.46)	0.593	_	
Wealth index in lowest 20%	0.92 (0.55–1.54)	0.746	_	

CI – confidence interval

households with high levels of malaria knowledge, derived from a principal components analysis, were nearly 3.5 times more likely to own a bednet compared to households with low levels of malaria knowledge, even after adjusting for potential confounders such as years of education and household wealth.

Multiple methods for categorizing and quantifying malaria knowledge have been used previously [10,11,15,20-22]. Most studies have used variations on a scoring system which provides points for correct answers to questions related to malaria knowledge and then categorizes respondents based on their scores. Hwang et al. in a study in Ethiopia [23] considered the use of principal components analysis for quantification of malaria knowledge but instead used a dichotomized scoring system comparing groups with no malaria knowledge (zero correct answers) to any correct malaria knowledge (≥1 correct answer). The authors justified such an approach because their result using the dichotomized score was equivalent to the principal components approach and was easier to interpret. Malaria knowledge in this Ethiopian cohort, however, was quite limited and only 4 knowledge questions were posed. In our study, participants answered correctly a mean of 7.1 out of 12 questions (standard deviation = 1.8) and there were no women who answered incorrectly to all. The bimodal distribution of Figure 2 supports our classification of malaria knowledge in 2 groups in our population, but the breadth of the questions we posed adds richness to our knowledge index.

Multiple village–, household– and individual–level characteristics have been associated with bednet ownership and use in a variety of bednet distribution settings, including education level, socio–economic status, perceptions of malaria risk and malaria knowledge. While some studies have found an increase in bednet ownership and use among those more knowledgeable about malaria [24,25], other studies have found little or no association [26,27].

Despite the association between malaria knowledge and bednet ownership in our study, an analysis of the individual components of our malaria knowledge index suggests important gaps in malaria knowledge in the sample. Only 73% of villagers replied that the primary means of acquiring malaria is from mosquitoes, 44% identified bednets as a means to protect against malarial fevers and only 67% of respondents identified children and 69% identified pregnant women as more vulnerable to malaria compared to adults or non–pregnant women, respectively. Finally, the prevailing view was that malaria was most common in the colder season, which is not typical for malaria in either Madagascar or in other sub–Saharan African settings and may represent overlap with perceptions of other causes of fevers.

Incorrect responses to questions about malaria are common in the literature, with heterogeneous levels of malaria knowledge across geographical and cultural settings. For example, a study in Tanzania among pregnant women in 2004 found nearly the opposite results: only 35% identified mosquitoes as the means of transmission of malaria and 91% reported bednets as a primary means of protection [10]. Our findings suggest that knowledge–based interventions should continue to be explored as a means to improve malaria bednet uptake, but the exact components of those interventions should account for the particular gaps in knowledge in a population given variations across, and potentially within, countries.

In addition to gaps in specific malaria knowledge, there were important gaps in optimal prevention behaviors. Only 8.2% of households owned a bednet. In addition, the presence of children under 5 years of age or pregnant women in the household was not associated with increased bednet ownership and only 53% of children under 5 years of age slept under a bednet the night before, even when the household owned a bednet (Table 3).

Higher wealth status, when categorized by quintile, was not associated with bednet ownership. This may seem unexpected in a setting where bednets are expensive relative to individuals' average income. Numerous studies, including an unpublished study from the region (Comfort and Krezanoski, in preparation), have shown that the price of bednets significantly affects the likelihood of households owning a bednet. Nevertheless, the absolute wealth of this population may be so low as to minimize relative differences in wealth in terms of ability to afford a bednet. In support of this interpretation, an examination of the wealth-index primary component scores (Figure 1) shows that the distribution is rightward skewed indicating that the majority of households are concentrated around a lower wealth level, with a small proportion of relatively affluent households.

In terms of assessing malaria knowledge, principal components analysis has the advantage of providing a means of comparison that is independent of the specific components making up that knowledge score. Principal components approaches also mitigate the problem of equally weighting responses about malaria knowledge, where, for example, sophisticated knowledge components, such as knowing that malaria can result in pregnancy loss, are given equal weight as basic components, such as knowing that malaria is transmitted by mosquitoes. Finally, our knowledge index measures each respondent relative to the study sample, allowing us to investigate how variations in malaria knowledge distinguish households from each other within a particular malaria–risk context.

Identification of malaria knowledge as a predictor of malaria prevention behaviors suggests a focus on malaria–specific education as a means of increasing bednet coverage even in settings without large scale distribution and subsidization of bednets [28,29]. However, questions remain as to the origins of the malaria knowledge measured in this study which appears correlated with household bednet ownership. In this study, respondents with higher levels of malaria knowledge had more education, confirming a correlation between formal schooling and health learning that has been found in previous studies [25,26]. The findings of higher malaria knowledge among respondents reporting that malaria is the most frequent or the most dangerous illness in the community and the association of higher malaria knowledge with female gender may be a marker of more frequent exposures to educational interventions delivered during prior treatment episodes for the individual or members of their family (especially children). This may be the result of health education occurring during health facility visits and reinforces the importance of interventions delivered during the evaluation and treatment of malaria episodes as a means of improving malaria prevention. Living in a higher wealth household was not associated with higher malaria knowledge, contrary to what may be expected through better access to formal education or exposure through media (radio, etc.) to health messages. Like bednet ownership, malaria knowledge in this population appears to be independent of relative household affluence.

Interpretations of these findings are subject to five limitations. First, we did not have an adequate sample size to examine the determinants of bednet use as opposed to ownership. The former is a much more relevant indicator for malaria prevention. Second, households that did not own nets were not asked if they desired a bednet nor were they asked about the perceived barriers to bednet ownership, including cost. Third, we assessed malaria knowledge only among one individual in the household (the survey respondent) and this respondent may or may not have equal impact on bednet ownership in the family, ie, less senior members. Nevertheless our main findings were consistent when restricting the analyses to the main decision making individuals (heads of households and their wives) within the household. Fourth, the local term for malaria, tazo moka ("fever from mosquitoes"), can be confused with tazo (general term for "fever"), thus there could have been misclassification of fevers not attributable to malaria. Finally, our survey did not ask participants about the primary source of their malaria knowledge nor did we perform qualitative studies to further explore the characteristics of their malaria knowledge. This information would help us determine whether malaria knowledge is coming from formal education, interactions with health workers or community health workers, media or from other sources.

CONCLUSIONS

In summary, in this secondary analysis of baseline data from 560 individuals participating in a randomized controlled trial in a setting without widespread access to bednets in rural Madagascar, we found that household knowledge of malaria was independently associated with an increased probability of bednet ownership. Higher levels of malaria knowledge were associated with reported concern about malaria as a common and dangerous illness in

the community as well as higher education and female gender, but were not associated with the wealth of the household. Further studies are warranted to elucidate the origins of better malaria knowledge and to determine how such knowledge may be best operationalized, possibly through education programs, to overcome the barriers to bednet ownership among at-risk households living outside the reach of large-scale distribution programs.

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Estimating the burden of neural tube defects in low– and middle–income countries

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Annie Lo Centre for Population Health Sciences The University of Edinburgh Medical School Teviot Place, Edinburgh EH8 9AG Scotland, UK a.lo@sms.ed.ac.uk **Background** To provide an estimate for the burden of neural tube defects (NTD) in low– and middle–income countries (LMIC) and explore potential public health policies that may be implemented. Although effective interventions are available to prevent NTD, there is still considerable childhood morbidity and mortality present in LMIC.

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Methods A search of Medline, EMBASE, Global Health Library and PubMed identified 37 relevant studies that provided estimates of the burden of NTD in LMIC. Information on burden of total NTD and specific NTD types was separated according to the denominator into two groups: (i) estimates based on the number of live births only; and (ii) live births, stillbirths and terminations. The data was then extracted and analysed.

Results The search retrieved NTD burden from 18 countries in 6 WHO regions. The overall burden calculated using the median from studies based on livebirths was 1.67/1000 (IQR=0.98-3.49) for total NTD burden, 1.13/1000 (IQR=0.75-1.73) for spina bifida, 0.25/1000 (IQR=0.08-1.07) for anencephaly and 0.15/1000 (IQR=0.08-0.23) for encephalocele. Corresponding estimates based on all pregnancies resulting in live births, still births and terminations were 2.55/1000 (IQR=1.56-3.91) for total NTD burden, 1.04/1000 (IQR=0.67-2.48) for spina bifida, 1.03/1000 (IQR=0.67-1.60) for anencephaly and 0.21 (IQR=0.16-0.28) for encephalocele. This translates into about 190000 neonates who are born each year with NTD in LMIC.

Conclusion Limited available data on NTD in LMIC indicates the need for additional research that would improve the estimated burden of NTD and recommend suitable aid policies through maternal education on folic acid supplementation or food fortification.

Every year, more than 300 000 children are born with neural tube defects (NTD) [1-6]. NTD are a group of congenital abnormalities that still cause hundreds of thousands of deaths in 0–4 years age group, while similar number of surviving children remain disabled for life [1-6]. One of the Millennium Development Goals initiated by the United Nations was dedicated to reducing global mortality rates of children in this age group. Since 1990, global child mortality has been declining largely due to the focus on communicable diseases, which included the expansion of immunisation programmes, promotion of breast–feeding and increased provision of mosquito bednets in many countries worldwide [2]. This reduc-

tion of mortality has led to the neglected causes of child mortality to be exposed, including that of congenital abnormalities [3-6].

NTD are one of the most common presenting birth defects, arising as a result of incomplete closure of the brain or spinal cord in the 3rd and/or 4th week of pregnancy [3]. NTD can be classified as open or closed, depending on whether neural tissues are exposed or covered by skin, respectively. Open NTD are more frequent and include spina bifida, an-encephaly and encephalocele. Closed NTD, such as tethered cord syndrome, are less frequent in comparison [4].

The best known risk factor for foetal NTD is maternal folate deficiency, arising from low levels of vitamin B9 (folic acid) [7,8]. Maternal vitamin B12 deficiency has only recently been shown to independently contribute to risk of NTD [9,10]. Additional risk factors for NTD development include a positive family history, smoking and indoor air pollution from coal and biomass heating used predominantly in developing countries [11-15]. Moreover, NTD are related to maternal socio–economic status, education, area of residence, and maternal nutrient deficiency or obesity [16,17].

NTD can be identified through simple prenatal testing using ultrasound imaging or maternal serum alpha–fetoprotein (MSAFP) level screening [18]. Abnormal elevation of MSAFP is a relatively specific and sensitive test for detection of NTD [18]. The abnormal presence of acetylcholinesterases (AChE) in amniotic fluid determined through amniocentesis can also be used for screening of NTD. However, a higher–than–normal test result is often not diagnostic and further evaluation should always be undertaken [19,20].

Since the discovery of folic acid as an effective intervention for prevention of neural tube defects [21], many countries have recommended folic acid intake before conception and during pregnancy. However, the dramatic 20% decrease in NTD birth burden after mandatory folic acid fortification (FAF) of enriched products in the US in 1998 showed that there may be more practical ways to administer this intervention [22]. Since this example, many countries such as Chile, Saudi Arabia and South Africa have implemented similar measures to staple food [23-25]. Despite folic acid being a well–known, cost–effective intervention, many developing countries continue to have either ineffective or no policy to increase maternal uptake of folic acid to prevent NTD.

The aims and objectives of this systematic review were:

- To provide an estimate of NTD burden in LMIC by systematically reviewing literature available in public domain;
- To examine and discuss the significance of these findings and consider clinical and cost–effective interventions and health policies with regards to NTD.

METHODS

A systematic literature review was conducted to search for published literature regarding population–based NTD burden estimates in LMIC, through the use of electronic databases: Medline, Embase, Global Health Library and PubMed. Potential further data were searched for on Google Scholar and by crosschecking reference lists from review articles. The search used Medical Subject Headings (MeSH) and key words for the burden of NTD in LMIC, as outlined by the World Bank. Limits of "human" and "2000– current" were used to obtain the most up to date NTD burden information. The last searches of the four databases were conducted on 6 February 2013. Search terms for Medline are shown in **Table 1** and were modified for other databases as required.

Table 1. Search terms for Medline

1.	exp Developing Countries/
2.	Developing countr*.tw
3. 4.	(developing adj3 countr*).tw africa/ or africa, northern/ or algeria/ or egypt/ or libya/ or moroc- co/ or tunisia/ or "africa south of the sahara"/ or africa, central/ or cameroon/ or central african republic/ or chad/ or congo/ or "dem- ocratic republic of the congo"/ or equatorial guinea/ 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 zam- bia/ or zimbabwe/ or benin/ or burkinafaso/ or cape verde/ or cote d'ivoire/ or gambia/ or ghana/ or guinea/ or guinea–bissau/ or li- beria/ or mali/ or mauritania/ or niger/ or nigeria/ or senegal/ or sierra leone/ or togo/ or americas/ or caribbean region/ or west in- dies/ or "antigua and barbuda"/ or bahamas/ or barbados/ or guate- torico/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "trinidad and tobago" or central america/ or belize/ or costa rica/ or el salvador/ or guatemala/ or honduras/ or paragua/ or panama/ or panama canal zone/ or latimamerica/ or maxico/ or south america/ or argentina/ or bolivia/ or brazil/ or chile/ or colombia/ or ecuador/ or frenchguiana/ or guyana/ or paraguay/ or peru/ or suriname/ or uruguay/ or venezula/ or ka- zakhstan/ or kyrgyzstan/ or tajikistan/ or turkmenistan/ or uzbeki- stan/ or laos/ or malaysia/ or mekong valley/ or myanmat/ or philippines/ or thailand/ or vietnam/ or bangladesh/ or bhutan/ or india/ or sikkim/ or middle east/ or afghanistan/ or sira/ or sil- anka/ or far east/ or china/ or tibet/ or "democratic people's repub- lic of korea"/ or mongolia/ or taiwan/ or albania/ or sil- anka/ or far east/ or china/ or tibet/ or "democratic people's repub- lic of korea"/ or mongolia/ or taiwan/ or albania/ or bintania/ or bosnia–herzegovina/ or bulgaria/ or "macedonia (republic)"/ or moldova/ or montenegro/ or romania/ or russia/ or sal- anda or mosteow/ or sibe
	atu/ or micronesia/ or palau/ or expsamoa/ or americansamoa/ or
	"independent state of samoa"/ or tonga/
5.	exp neural tube defects/ or anencephaly/ or arnold-chiari malfor-
	mation/ or encephalocele/ or meningocele/ or meningomyelocele/ or "pentalogy of cantrell"/ or exp spinal dysraphism/ or nervous system malformation

_		system malformation
_	б.	"neural tube defect".tw
_	7.	"neural tube defects".tw
	8.	NTD.tw
_	9.	exp Prevalence/
	10.	prevalen*.tw
	11.	1 or 2 or 3 or 4
_	12.	5 or 6 or 7 or 8
	13.	9 or 10
	14.	11 and 12 and 13
	15.	Limit 14 to (humans and yr="2000 –Current")

Study selection

The inclusion criteria for relevant papers included population or hospital based studies conducted in LMIC, which were geographically defined taking into account both the World Health Organization's and the World Bank's classification and treating any discrepancies in an inclusive, rather than exclusive way. The studies needed to have clearly expressed NTD burden showing a denominator, published between 2000 and 2013. The searches were limited to the period after the year 2000 in order to generate an estimate that is reflective of reasonably recent NTD trends. No limit on language and publication type was set. Keeping in mind that many babies with NTD are stillborn or terminated through miscarriages and abortions, we decided to include studies with live births, stillbirths and terminations as a separate body of evidence, in addition to studies that used live births-based denominators to report the burden of NTD.

Studies conducted solely in specialist hospital units were excluded, as they are likely to report a burden enriched for severe cases that would not be representative of the general population. Studies with incomplete data or where NTD burden could not be calculated were also excluded.

Data extraction

For the 37 retained studies, relevant data were extracted and compiled into Microsoft Excel spreadsheets. Data including authors, country, study size and diagnostic criteria for specific NTD type and total NTD cases were extracted. Types of NTD included spina bifida, myelomeningocele, meningocele, anencephaly, encephalocele and "other NTD types". Burden was expressed using the number of cases observed and a total sample of live births (or, alternatively, a total sample of live births, stillbirths and terminations).

Data analysis

When the number of affected children was not specifically provided in the study, it was calculated with the sample population using the following equation:

Estimated NTD burden=Number of observed NTD cases/ Sample size (eg, number of live births)×1000

The estimates of the burden provided in the retained studies were separated into two categories: those in which the denominator was based on the number of live births, and the other group in which live births, stillbirths and terminations were all included. Wherever this information was available for both categories, figures were separately added to the respective groups. The median estimate of the NTD burden and the inter–quartile range (IQR) for all LMIC regions was then determined, based on the retained 37 studies. Eventually, the median was multiplied by the number of livebirths in LMIC in the year 2010, according to UN Population Division's estimates (www.un.org/esa/population/), to determine the absolute number of NTD cases that has been introduced to the LMIC in 2010.

RESULTS

A review of relevant databases performed independently by two researchers (AL and SS) identified a total of 3339 studies, but only 37 satisfied all criteria for inclusion (as shown in **Figure 1**). Of the retained studies, 20 reported NTD rates in live births only, 14 reported rates in live births, stillbirths and terminations combined, and 3 studies reported both.

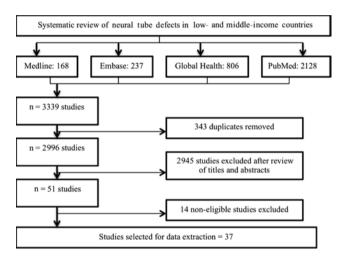


Figure 1. A summary of the process of literature search.

The median sample size from all reviewed papers was 36331, which corresponded well to a typical study size. The median sample population in studies based on live births was 35974, compared to 49534 in studies based on live births, stillbirths and terminations.

The search retrieved NTD burden from 18 countries in 6 WHO regions (Table 2). The overall burden calculated using the median from studies based on live births was 1.67/1000 (IQR=0.98-3.49) for total NTD burden (Table 3 and 4), 1.13/1000 (IQR=0.75-1.73) for spina bifida (Table 3 and 5), 0.25/1000 (IQR=0.08-1.07) for an encephaly (Table 3 and 6) and 0.15/1000 (IQR=0.08-0.23) for encephalocele (Table 3 and 7). Corresponding estimates based on all pregnancies resulting in live births, still births and terminations were 2.55/1000 (IQR=1.56-3.91) for total NTD burden (Table 3 and 8), 1.04/1000 (IQR=0.67-2.48) for spina bifida (Table 3 and 9), 1.03/1000 (IQR=0.67-1.60) for an encephaly (Table 3 and 10) and 0.21 (IQR=0.16-0.28) for encephalocele (Table 3 and 11). This translates into about 190 000 neonates who are born each year with NTD in LMICs.

Table 2. Distribution	of retained s	studies by W	/HO regions
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				0
		Number of studies		IF STUDIES
WHO REGION	Country	Total studies	Live Births Only	Live births, stillbirths & terminations
Western Pacific	China	6	1	5
western Pacific	Malaysia	1	0	1
	India	3	2	1
South East Asia	Pakistan	1	1	0
	Thailand	1	1	0
	Jordan	2	2	0
Eastern Mediterranean	Saudi Arabia	2	2	0
	Iran	4	1	3
	Azerbaijan	1	0	1
Europa	Russia	1	1	0
Europe	Ukraine	1	0	1
	Turkey	3	2	1
Africa	Cameroon	1	1	0
Amca	South Africa	1	1	0
	Brazil	3	2	1
Amoricas	Colombia	1	1	0
Americas	Peru	1	1	0
	Chile	4	1	3

As expected, when comparing IQRs as the robust predictions, overall NTD burden estimates were found to be higher in the live births, stillbirths and terminations group in comparison to studies that included only live births, while spina bifida was the most commonly reported NTD type. Moreover, there is internal consistency in the presented estimates, because the sum of the specific NTD types always fits into the "envelope" of all NTDs.

DISCUSSION

This systematic literature review aimed to examine the burden of NTD in LMIC. It is, to our knowledge, the first study to quantitatively estimate the total NTD burden in LMIC. As such, the burden estimates can be successfully used in the much–needed preventive policy development in LMIC with high risk of NTD.

The results from the 37 selected studies [10-13,23-55] suggest that NTD burden is approximately twice as high, if not higher, in LMIC than in high—income countries [56-58]. The findings from live birth—only studies showed that the median total NTD burden is 1.67 per 1000 live births, although there were reports of significantly higher values, with a maximum burden as high as 12.41/1000. The overall median is greater in studies where live births, stillbirths and terminations were taken into account, where the bur-

Table 4. Studies that reported rates for total NTD burden based	L
on live births only	

AUTHOR AND REFERENCE	Sample size	Cases	Rate (per 1000 live births)			
Amarin et al. [26]	61447	16	0.95			
Aqrabawi [11]	5088	33	6.50			
Asindi et al. [27]	82176	64	0.78			
Bademci et al. [28]	5499	17	3.09			
Behrooz et al. [29]	13262	56	4.22			
Chen et al. [30]	26599	48	1.80			
Cherian et al. [31]	1218	10	8.21			
Cortes et al. [32]	59627	67	1.12			
Costa et al. [33]	9386	11	1.17			
Gu et al. [13]	6420	25	3.89			
Hertrampf et al. [34]	117740	114	0.97			
Kaur et al. [35]	7400	5	0.68			
Khattak et al. [36]	5560	69	12.41			
Mandiracioglu et al. [37]	36331	56	1.54			
Njamnshi et al. [38]	52710	98	1.86			
Pachajoa et al. [39]	32 995	55	1.67			
Petrova et al. [40]	141159	298	2.11			
Pacheco et al. [41]	24964	124	4.97			
Ricks et al. [42]	35974	72	2.00			
Safdar et al. [24]	33489	42	1.25			
Sayed et al. [25]	46021	45	0.98			
Wasant et al. [43]	180 000	114	0.63			
Yuskiv et al. [33]	75609	38	0.50			

den is 2.55 per 1000 and maximum reported burden of 19.94/1000. This is expected, as a considerable proportion of NTD result in stillbirths and terminations [59,60].

Significant discrepancies between reported burdens from the same country were sometimes observed. These differences were attributed to different study settings, for example in rural and urban India [31,35,45], or different time periods as seen in two studies from Jordan [11,26]. Extremely high burden of NTD of 13.79 and 19.94 was observed in two studies from China, although the samples were rather small, indicating a possible selection bias [10,13].

Regardless of the progress in control of NTDs observed in high–income countries, NTD continue to be a problem of significant public health impact in LMIC. NTD have detrimental physical and emotional effects on the affected children and their caregivers, and may present a life–long important and often insurmountable economic problem, especially to poor families [52]. The cost of raising a child with spina bifida from birth to 18 years of age in Chile was estimated to be around US\$ 120 000 [34]. These expenses, apart from causing individual deprivation, are a significant economic burden on the level of the whole society, causing a vicious circle of poverty in the LMIC.

 Table 3. A summary of estimates of the burden of neural tube defects and its sub-types from 37 retained studies from low and middle-income countries

Studied outcome	Denominator	Number of Studies	Median (per 1000)	Inter-QUARTILE RANGE (PER 1000)	Minimum(per 1000)	Maximum (per 1000)
All neural tube defects	LB	23	1.67	0.98-3.49	0.50	12.41
All neural tube defects	LB+SB+TP	17	2.55	1.56-3.91	0.86	19.94
Spine hifde	LB	14	1.13	0.75-1.73	0.38	5.90
Spina bifida	LB+SB+TP	15	1.04	0.67-2.48	0.35	5.81
Anencephaly	LB	13	0.25	0.08-1.07	0.01	11.33
Allelicephary	LB+SB+TP	16	1.03	0.67-1.60	0.30	8.26
F 1 1 1	LB	9	0.15	0.08-0.23	0.03	0.39
Encephalocele	LB+SB+TP	13	0.21	0.16-0.28	0.07	2.65

LB - live births; LB+SB+TP - live births, stillbirths and terminated pregnancies

Table 5. Studies that reported rates for the burden of spina bifida based on live births only

Author and reference	SAMPLE SIZE	Cases	Rate(per 1000 live births)
Aqrabawi [11]	5088	30	5.90
Asindi et al. [27]	82176	46	0.56
Bademci et al. [28]	5499	11	2.00
Behrooz et al. [29]	13262	23	1.73
Cherian et al. [31]	1218	6	4.93
Costa et al. [44]	9386	7	0.75
Khattak et al. [36]	5560	5	0.90
Mandiracioglu et al. [37]	36331	43	1.18
Njamnshi et al. [38]	52710	65	1.23
Petrova et al. [40]	141159	147	1.04
Ricks et al. [42]	35974	62	1.72
Safdar et al. [24]	33489	36	1.07
Sayed et al. [25]	46021	25	0.54
Yuskiv et al. [33]	75609	29	0.38

Table 6. Studies that reported rates for the burden of anencephaly based on live births only

Author and reference	Sample size	CASES	RATE (PER 1000 LIVE BIRTHS)
Asindi et al. [27]	82176	3	0.04
Behrooz et al. [29]	13262	30	2.26
Cherian et al. [31]	1218	3	2.46
Costa et al. [44]	9386	1	0.11
Khattak et al. [36]	5560	63	11.33
Mandiracioglu et al. [45]	36331	4	0.11
Njamnshi et al. [38]	52710	4	0.08
Petrova et al. [40]	141159	151	1.07
Ricks et al. [42]	35974	10	0.28
Safdar et al. [24]	33 489	1	0.03
Sayed et al. [25]	46021	17	0.37
Wasant et al. [43]	180000	45	0.25
Yuskiv et al. [33]	75609	1	0.01

Hundreds of thousands of live born babies are affected by NTD in LMIC, which remain an important and preventable cause of morbidity and mortality. Thus, effective policies for prevention are vital to reduce the burden of NTD on individuals and on society. Up to now, more than 59 countries have committed to mandatory fortification programmes [59,61,62]. However, many LMIC still have ineffective recommendations and policies towards folic acid uptake. Some countries have recommended the improvement of daily diet and folic acid supplement use, but do not have a mandatory policy [59,61,62]. Recommendation provides a good starting point for reducing NTD burden in LMIC. However, many households in LMIC may not be able to afford folic acid supplementation throughout pregnancy [63]. As shown by the example from the US where NTD burden had fallen by 20% after mandatory fortification, recommendation alone, even without the economic constraint, is not likely to provide a feasible and effective solution [22]. Interestingly, survey conducted in the UK found that there was only a marginal increase in folic acid intake in women who were planning pregnancy [64]. Additionally, around half of all pregnancies in the US are unexpected [58,62], and this figure may be even higher in LMIC where there may be limited availability of contraception.

Despite obvious benefits, before promoting folic acid fortification, many factors must be considered. Currently no country in the European Union has compulsory fortification schemes due to risk consideration and campaigns

Table 7. Studies that reported rates for the burden of encepalocele based on live births only

Author and reference	SAMPLE SIZE	Cases	Rate (per 1000 live births)
Agrabawi [11]	5 088	7	0.39
Asindi et al. [27]	82 176	15	0.18
Behrooz et al. [29]	13262	3	0.23
Costa et al. [44]	9 386	3	0.32
Mandiracioglu et al. [45]	36331	1	0.03
Njamnshi et al. [38]	52710	5	0.09
Safdar et al. [24]	33 489	5	0.15
Wasant et al. [43]	180 000	14	0.08
Yuskiv et al. [33]	75 609	3	0.03

Table 8. Studies that reported rates for total NTD burden based on live births, stillbirths and terminations of pregnancy

Author and reference	Sample size	Cases	RATE (PER 1000 LIVE BIRTHS STILLBIRTHS AND TERMINATIONS)
Aguiar et al. [46]	18807	89	4.73
Cortes et al. [32]	60072	94	1.56
Cortes et al. [12]	486779	419	0.86
Dai et al. [46]	2281616	2873	1.30
Golalipour et al. [47]	37951	109	2.87
Golalipour et al. [12]	30639	78	2.55
Golalipour et al. [48]	49534	194	3.91
Gu et al. [13]	6420	128	19.94
Li et al. [10]	11534	159	13.79
Liu et al. [49]	99888	122	1.22
Mahadevan et al. [45]	54738	310	5.66
Nazer et al. [50]	434624	740	1.70
Noraihan et al. [51]	34109	37	1.08
Onrat et al. [52]	8631	31	3.59
Rad et al. [53]	14121	117	2.57
Yuskiv et al. [33]	75928	159	2.09
Zhang et al. [54]	62373	126	2.02

Table 9. Studies that reported rates for the burden of spina bifida

 based on live births, stillbirths and terminations of pregnancy

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Author and reference	Sample size	Cases	Rate (per 1000 live births, stillbirths and terminations)
Cortes et al. [32]	60072	46	0.77
Cortes et al. [12]	486779	204	0.42
Golalipour et al. [47]	37951	62	1.63
Golalipour et al. [12]	30639	39	1.27
Gu et al. [13]	6420	25	3.89
Li et al. [10]	11534	67	5.81
Liu et al. [49]	99888	59	0.59
Mahadevan et al. [45]	54738	170	3.11
Noraihan et al. [51]	34109	12	0.35
Onrat et al. [52]	8631	9	1.04
Yuskiv et al. [33]	75928	64	0.84
Aguiar et al. [55]	18807	47	2.49
Dai et al. [46]	2281616	1369	0.60
Nazer et al. [50]	434624	374	0.86
Rad et al. [53]	14121	35	2.48

Table 10. Studies that reported rates for the burden of an encephaly based on live births, stillbirths and terminations of pregnancy

AUTHOR AND REFERENCE	Sample size	Cases	RATE (PER 1000 LIVE BIRTHS, STILLBIRTHS AND TERMINATIONS)
Aguiar et al. [55]	18807	24	1.28
Cortes et al. [32]	60072	37	0.62
Cortes et al. [12]	486779	147	0.30
Dai et al. [46]	2281616	1140	0.50
Golalipour et al. [47]	37951	43	1.40
Golalipour et al. [12]	30639	35	0.92
Golalipour et al. [48]	49 5 34	56	1.13
Gu et al. [13]	6420	53	8.26
Li et al. [10]	11534	75	6.50
Liu et al. [49]	99888	42	0.42
Mahadevan et al. [45]	54738	98	1.80
Nazer et al. [50]	434624	311	0.72
Noraihan et al. [51]	34109	25	0.73
Onrat et al. [52]	8631	12	1.39
Rad et al. [53]	14121	78	5.52
Yuskiv et al. [33]	75928	62	0.82

Table 11. Studies that reported rates for the burden of encephalocele based on live births, stillbirths and terminations of pregnancy

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Author and reference	Sample size	Cases	RATE (PER 1000 LIVE BIRTHS STILLBIRTHS AND TERMINATIONS)
Aguiar et al. [55]	18807	5	0.27
Cortes et al. [32]	60072	11	0.18
Dai et al. [46]	2281616	365	0.16
Golalipour et al. [47]	37951	4	0.11
Golalipour et al. [12]	30639	4	0.13
Gu et al. [13]	6420	17	2.65
Li et al. [10]	11534	17	1.47
Liu et al. [49]	99888	7	0.07
Mahadevan et al. [45]	54738	36	0.66
Nazer et al. [50]	434624	91	0.21
Onrat et al. [52]	8631	2	0.23
Rad et al. [53]	14121	4	0.28
Yuskiv et al. [33]	75928	12	0.16

against 'mass medication' [65,66]. Safety, ethics and economic feasibility of a FAF programme must be taken into account before implementing such a policy, especially on a whole–country level. Nevertheless, current high burden of NTD in LMIC stresses the need for a comprehensive prevention program.

For consistent and reliable estimates on burden of NTD, it is important to set up vital and birth registration documentation programs in countries that lack coherent information on NTD burden. Not only will this aid in the prevention and treatment of NTD, but it will also enable policy makers to monitor the benefits of implemented prevention programs. This may be particularly important for countries in the African WHO region, where a high NTD burden is expected, but from which only a few studies have been published [67,68]. The reported NTD burden was estimated based on a limited number of available studies, some with very variable sample sizes that differed in inclusion of stillbirths and terminated births in the study design. We could not use meta– analysis, because studies came from such heterogeneous contexts that we didn't feel it was justified to present anything beyond simple median and IQR in this initial estimate. This is partly because not all studies adhered to ICD–10 classification of NTD and were not uniformly conducted regarding method of diagnosis and reporting of NTD type, enabling potential over– or under–estimation of NTD burden through misdiagnosis. Also, the technical restrictions of accounting for all stillbirths and terminations in the examined studies limited the precision of our estimated burden in that population [68].

Finally, the data was available from studies conducted in only 18 countries, implying that the studied sample is unlikely to be representative of all the LMIC globally. Regardless of these significant limitations, it is our opinion that the estimated burdens reported in the results provide useful data for initial assessment of NTD burden in LMIC. An increase in high quality research on NTD, especially with regards to gender and geographical regions, should be prioritised to allow more accurate NTD estimates. This would make the burden of the problem easier to estimate in a more credible way, and allow effective planning of prevention and intervention to minimise the risks for NTD.

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Evidence for localised HIV related micro– epidemics associated with the decentralised provision of antiretroviral treatment in rural South Africa: a spatio–temporal analysis of changing mortality patterns (2007–2010)

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Paul Mee Visiting Researcher MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt) School of Public Health University of the Witwatersrand South Africa paul.mee@wits.ac.za **Background:** In this study we analysed the spatial and temporal changes in patterns of mortality over a period when antiretroviral therapy (ART) was rolled out in a rural region of north–eastern South Africa. Previous studies have identified localised concentrated HIV related sub–epidemics and recommended that micro–level analyses be carried out in order to direct focused interventions.

Methods Data from an ongoing health and socio–demographic surveillance study was used in the analysis. The follow–up was divided into two periods, 2007–2008 and 2009–2010, representing the times immediately before and after the effects on mortality of the decentralised ART provision from a newly established local health centre would be expected to be evident. The study population at the start of the analysis was approximately 73 000 individuals. Data were aggregated by village and also using a 2×2 km grid. We identified villages, grid squares and regions in the site where mortality rates within each time period or rate ratios between the periods differed significantly from the overall trends. We used clustering techniques to identify cause–specific mortality hotspots.

Findings: Comparing the two periods, there was a 30% decrease in age and gender standardised adult HIV–related and TB (HIV/TB) mortality with no change in mortality due to other causes. There was considerable spatial heterogeneity in the mortality patterns. Areas separated by 2 to 4 km with very different epidemic trajectories were identified. There was evidence that the impact of ART in reducing HIV/TB mortality was greatest in communities with higher mortality rates in the earlier period.

Conclusions: This study shows the value of conducting high resolution spatial analyses in order to understand how local micro–epidemics contribute to changes seen over a wider area. Such analyses can support targeted interventions.

South Africa is one of the countries worst affected by the HIV pandemic. In 2011 there were estimated to be 5.6 million people infected with HIV, with an HIV prevalence of 17.6% for those aged between 15 and 49 [1].

In recent years the outlook for those infected has improved considerably with the percentage of those requiring antiretroviral treatment (ART) who are receiving the drugs increasing from 30% in 2009 [2] to 75.2% in 2011 [3]. The impact of ART programmes in reducing HIV related mortality and increasing life expectancy has been reported in a number of studies in sub–Saharan Africa [4–7]. However, the analysis of trends at a national, regional or district level may mask important local variations. It is important to understand this micro-level variation in order to effectively target interventions [8–12] as behaviours linked to higher or lower risk may be clustered in local communities [13,14]. The data required for such detailed analyses are often only available in sites where the dynamics of a population can be followed in detail over time. Hence, Health and Demographic Surveillance Sites (HDSSs) provide the ideal platform for such analyses. [15,16]. Wand and Ramjee [10,11,14] identified local high prevalence spatial clusters of HIV and sexually transmitted infections amongst women in the Greater Durban area of Kwa Zulu Natal in South Africa. Tanser and colleagues [12] reviewed data from studies in various sub-Saharan African countries to provide evidence for the likely benefit of targeted interventions aimed at high risk groups to supplement more general population level approaches to HIV prevention.

Here we describe changing spatial patterns in the local development of an HIV epidemic over a period of time during which a health centre was established in order to test and treat those infected with HIV in addition to providing general health care for the local community. The goal of this analysis was to gain an understanding of which communities and sub-communities have benefitted preferentially from the enhanced access to treatment and those for which the situation may have deteriorated. By use of a grid overlay we were able break down communities into smaller subunits and calculate cause-specific mortality trends in each of the grid squares. We also used clustering techniques to obtain complementary information on areas and periods of time where mortality risks differed from those expected. Clustering methods have been used previously to investigate HIV related mortality patterns in a rural South African setting, indicating the value of the technique in identifying locations for targeted interventions [8,17]. Using these multiple methodologies we were able to gain a fine grained understanding of the localised epidemic dynamics.

METHODS

Location of the study

This study was carried out in the Agincourt Health and Socio–Demographic Survey site (AHDSS) located in the Bushbuckridge sub–district of Ehlanzeni municipality of Mpumalanga province in South Africa. [18] The site runs alongside the Kruger National Park and is close to the border with Mozambique (Figure 1). Approximately one third of the population are of Mozambican ethnic origin, mainly refugees from the Mozambican civil war. A number of the pre–existing villages gave over land in which 'Mozambican' settlements were established. These were initially characterised as having poorer levels of infrastructure and greater poverty than the established villages [19]. These former refugee communities are mainly located in the eastern part of the study site.

The area is predominantly rural though close to a number of peri–urban settlements. It is characterised as having high unemployment, a high level of poverty and relatively poor levels of educational attainment [18]. This has resulted in a high level of out–migration for economic reasons. Often the migrants retain strong connections with their original households and financial remittances from migrants are an importance source of income [20].

The baseline census for the AHDSS was carried out in 1992, and the present annual cycle of household follow– up visits was established in 1999. In 2007 the study site population was approximately 73 000 individuals. In order to maintain anonymity alphabetical identifiers rather than names are used to identify the villages in this study.

Population distribution

The study site is made up of discretely bounded villages (Figure 2). Central areas of the villages often have a maximum population density greater than 1000 people/km² which is more typical of an urban area in this region. The northern portion of the study site generally has a lower population density than the western and central parts.

ART and VCT provision in the Agincourt site

Effective ART became available worldwide in the mid 1990s. In South Africa, however, the treatment only be-



Figure 1. The location of the Agincourt HDSS in the South Africa and the surrounding region.

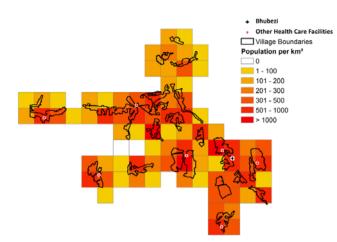


Figure 2. Mean population densities within the study site, 2007–2010.

came available in the public sector in 2004 [2]. Subsequently there were delays in rolling out ART across the country particularly in rural areas such as that in which the Agincourt HDSS is located.

In 2002 a programme was introduced to provide voluntary counselling and HIV testing (VCT) services in the 5 health centres operating in the study area [21]. Prior to this VCT had only been available outside the site. Two of the secondary level hospitals serving the population in the study site began to provide ART treatment between 2004 and 2005. To improve clinic access a programme of decentralisation of ART services began in 2008 when a clinic in the study site (Agincourt) and another in a peri–urban settlement (Thulamahashe) just to the west of the site started to provide ART. At the same time a community health centre, Bhubezi, initially operating outside the public sector and providing general health care with an emphasis on HIV testing and treatment was established. Throughout this period ART was available from private providers.

This study examines changes in mortality in two consecutive time periods 2007–2008 and 2009–2010 the periods immediately before and after the possible effects on mortality of the decentralised ART provision from the Bhubezi health centre would be expected to be evident.

Data used in the study

The core information captured in the annual AHDSS rounds were updates of the residency status and vital information for all household members. This was collected by interviewing the most knowledgeable available representative. For all deaths reported, a detailed verbal autopsy (VA) interview was carried out. The latitude and longitude of every dwelling was captured. Residents of two villages which were added to the site in 2009 were excluded from the analysis. The study population was restricted to males and females aged 15 years and above.

Cause of death (CoD) was assigned using the InterVA–4 model [22,23]. The InterVA–4 input variables are based on the questions in the standardised World Health Organisation (WHO) VA instrument released in 2012 [24]. A computer implementation of the InterVA–4 probabilistic model is freely available for download from http://www.interva. net. InterVA–4 uses a Bayesian probabilistic technique to calculate the likelihood of a particular cause of death for an individual based upon the presence or absence of particular signs or symptoms. An important advantage of the InterVA model over clinicians' assessments is the consistency in cause of death ascertainment over time. A multicentre validation study of the InterVA–4 model against known HIV serostatus has shown good validity [25].

The variables required for the InterVA–4 input were derived from the responses given to the Agincourt VA questionnaire. In addition to directly matching variables, key words or phrases from narrative fields which were specifically associated with InterVA–4 input variables were identified. To overcome misspelling in the narratives, a string similarity matching algorithm (Jaro–Winkler) [26] was applied to identify similar strings, a cut–off score of 0.9 was used to define a match. These matches were checked manually. The matching algorithms were programmed using routines implemented in T–SQL, the proprietary implementation of the SQL standard in the SQL*Server[™] 2008 software package. [Microsoft Corporation, Redmond, Washington USA].

Figures from 2009 [27] indicate that around 70% of those infected with tuberculosis are co–infected with HIV in South Africa. Due to this high level of co–morbidity deaths due to HIV–related disease (WHO VA code –01.03 HIV/ AIDS related death) and pulmonary tuberculosis (WHO VA code –01.09) were joined in a single category, HIV/TB. All other deaths for which a CoD was available were categorised as non–HIV/TB.

Analytical approach

Mortality rates were directly standardised by age and gender in each 2-year period using the age/gender proportions of the entire site in the relevant period as the standard. The adult population was subdivided into 3 categories for the standardisation; 15 to 49, 50 to 65 and over 65. The standardised rates and the associated 90% confidence intervals (CI) were calculated using Stata, version 10.0 SE (Stata Corp., College Station, Texas, USA). Chi–Squared values and Student T–tests were used to compare the effect of indeterminate cause of death data.

An initial comparison of mortality patterns aggregated the individuals into their villages of residence. This approach was based on that of previous studies [28,29] where mortality clusters were identified using village centroids. A rationale for this approach is that within the study site each village is geographically isolated from the others with its

own leadership which to some extent can influence local characteristics. However there is also likely to be intra-village heterogeneity which such an analysis may not identify. A study of national HIV prevalence data in South Africa [9] emphasised the danger in aggregating data only by province as this led to a loss of understanding of localised prevalence levels for communities which crossed provincial boundaries. A similar problem exists with village-level aggregation. For this reason, a grid was created extending across the site. After investigating various grid sizes a 2×2 km grid was chosen in order to give reasonable numbers of deaths and strata-specific populations in each square. A previous study of mortality patterns in the Butajira HDSS site in Ethiopia used a similar approach in order to get a more fine grained understanding of spatio-temporal mortality patterns [30].

The person years at risk were calculated for each individual in each of the two year time periods using the start of the period to begin the residence episode and either an end event, out-migration, death or the end of the period to right–censor the person time accrued. Mortality rate ratios were calculated for each grid square or village. In the grid analysis, if the lower bound of the 90% CI of the rate or rate ratio was higher than the mean value for the site that was classified as a significantly high value. Similarly if the upper bound was less than the mean this was classified as a grid square with a significantly low value. The grid and population density maps were developed using the ArcGIS software (ESRI 2011. ArcGIS Desktop: Release 10. Redlands, CA: Environmental Systems Research Institute). Other studies have suggested that lengthy travel times to clinics can provide a significant barrier to access [31–33], conversely better road links may also lead to greater opportunities for social mixing and hence a higher risk of exposure to infection [8]. Hence we assessed the proximity of areas of high or low mortality rates or rate ratios to the clinics and roads.

Spatio-temporal cluster analysis was carried out using Kulldorff's spatio-temporal scan statistic as implemented in the SaTScanTM software v9.1 to identify the location and evaluate the statistical significance of spatial and temporal clusters of mortality [34]. In this analysis a cylindrical scanning window is moved across the study area, so that each location of the window captures a unique set of individuals during a specific range of dates. The radius of each cylinder is allowed to vary. The height of the cylinder corresponds to a specific range of dates. To evaluate statistical significance, a comparison is made between the number of cases (eg, cause specific deaths) within the scanning window and the number of cases outside of that window using a maximum likelihood ratio test statistic. The centre of the scanning window moves in geographical space and time allowing significant high or low clusters of deaths in space and/or time to be identified. The population at each dwelling was derived from the total number of person years rounded to the nearest integer value with a minimum value of 1. The dates of death were aggregated by month. The maximum spatial and temporal windows used were 50% of the population at risk and 50% of the entire period (2 years) respectively. A Poisson probability model with a maximum of 999 Monte–Carlo replications was used in the analysis. A cut–off *P* value of 0.2 was used to identify clusters of interest.

In order to obtain an objective measure of the degree of spatial homogeneity in the pattern of rate ratios, a calculation was made of the Global Moran's I statistic using the GeoDa software [35]. A distance weight matrix was created using rook contiguity to indicate the nearest neighbours associated with a particular grid square. A Global Moran's I statistic of close to zero indicates a random spatial distribution, values approaching +1 or -1 indicate that there is overall a high degree of spatial correlation.

FINDINGS

Between 2007 and 2010, 3660 deaths were recorded in the study site. Of these, 567 (15.5%) were excluded from the analysis as a cause of death could not be assigned due to either the initial verbal autopsy not having been carried out or there being a lack of symptomatic data. For the remaining deaths, 2584 occurred in those aged 15 years and over. A further 13 deaths were excluded from the grid analysis as no geographical coordinates for the place residence of these individuals were available.

To assess the possible effects of indeterminate causes of death, an analysis was carried out of the spatial distribution of deaths with and without a CoD assignment for the entire study population. The spatial separation of the centroids of the home residences for the two categories was 464 m indicating that there was no significant spatial bias introduced. The percentage of indeterminate CoD assignments was greater in 2009 to 2010 than in 2007 to 2008 (16.3% compared with 15.7%, P=0.014). There were more indeterminate CoDs for males than females (17.2% compared with 14.2%, P=0.012). Also those with indeterminate CoDs were on average younger than those for whom a cause of death was assigned (36.7 years compared to 42.5 years, P<0.001)

Village level analysis of mortality

HIV/TB mortality. There was a large range of values for the standardised mortality rates (SMRs) for HIV/TB during both time periods (see Table S1 in the Online Supplementary Document). The rate ratio between the latter and earlier period was 0.70 (90% CI=0.64–0.77) indicating a decrease in the HIV/TB mortality rates of between 23% and 36% with a point estimate of 30%. The rate ratios (RR) for individual villages are shown in Figure 3.

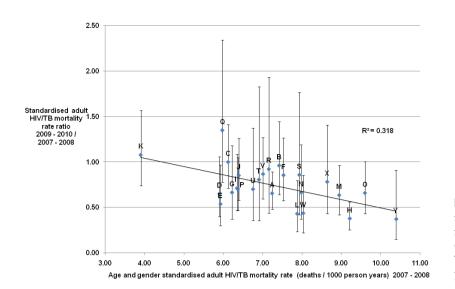


Figure 3. A comparison of the HIV/TB mortality rate ratios (with 90% confidence intervals) and mortality rates for 2007–2008 (points are labelled with the village codes). The best fit trend line is superimposed on the points with the associated R–squared value.

A rate ratio greater than 1 indicating an increase in the adult HIV/TB mortality rates was seen for two of the twenty—five villages (Q and K.) For twenty—two villages a decrease in the HIV/TB mortality rates were seen. However, for fourteen of these the upper bound of the 90% CI was greater than or equal to 1 indicating that the evidence for a decrease was weak. For one village the HIV/TB mortality rate remained unchanged.

Village Q had the highest rate ratio value of 1.35 (90% CI = 0.78-2.34) indicating a point estimate of a 35% increase in the HIV/TB mortality rate, as the lower bound of the confidence interval is less than 1 it is possible that there was a trend towards a decrease in the rate over the period. The lowest HIV/TB mortality rate ratios were 0.37 (90% CI = 0.15-0.91) for village Y, 0.38 (90% CI = 0.26-0.56) for village H and 0.43 (90% CI = 0.23-0.80) for village L, in each case the upper bound of the confidence interval is less

than 1 indicating a rate decrease to be a reasonable interpretation. Villages H and L are geographically close neighbours to village Q.

The gradient of the trend line fitted to the plotted points (Figure 3) was 0.091, indicating a decrease of close to 9% in the mortality rate ratio between the two periods for each unit increase in the mortality rate in the earlier period. The low R² value of 0.318 showed that there was a significant amount of variation around this overall trend.

Non–HIV/TB mortality. Similar to HIV/TB deaths, there were large variations between villages in the SMRs for deaths due to causes oth-

er than HIV/TB during both time periods (see Table S2 in the Online Supplementary Document). The standardised adult rate ratio for non–HIV/TB mortality between 2007 to 2008 and 2009 to 2010 was 1.01 (90% CI=0.92–1.10) indicating that there was no overall change evident in the non HIV/TB mortality rates for adults between the two periods. The range in rate ratios was from 0.42 (90% CI=0.25–0.71) for village N to 1.84 (90% CI=1.19–2.86) for village W. With the upper bound of the rate ratio for village N less than 1 and the lower bound for village W greater than 1 it is reasonable to interpret this as evidence for significantly different changes in cause–specific rates between the two.

The graph in Figure 4 shows a decrease in the rate ratio as the initial mortality rate increases with a gradient of 0.110 for the trend line. The R² value of 0.361 again indicates significant variation around the overall trend.

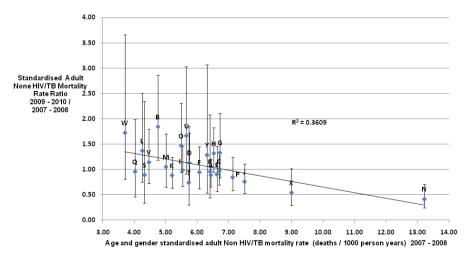


Figure 4. A comparison of the Non HIV/TB mortality rate ratios (with 90% confidence intervals) and mortality rates for 2007–2008 (points are labelled with the village codes). The best fit trend line is superimposed on the points with the associated R–squared value.

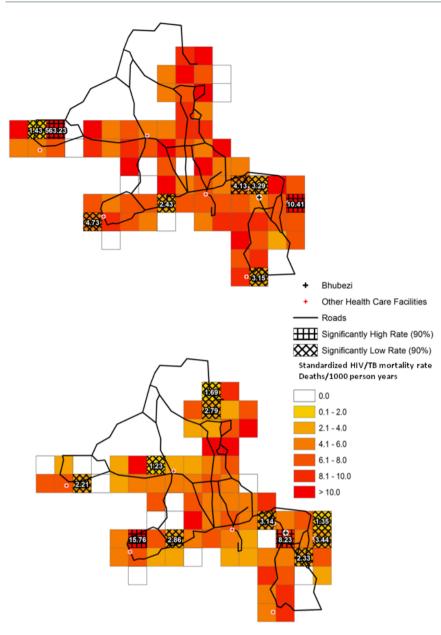


Figure 5. HIV/TB mortality rates (deaths per 1000 person-year, PY) from 2007 to 2008 (upper panel) and 2009–2010 (lower panel) in 2 km grid squares for the Agincourt HDSS site. For grid squares with significantly low rates, the upper bound of the 90% confidence interval is less than the mean rate. For grid squares with significantly high rates the lower bound of the 90% confidence interval is greater than the mean rate. The label is the mortality rate for the grid square.

Gridded mortality plots

HIV/TB mortality. Figure 5 shows the HIV/TB mortality rates in each grid square for 2007 to 2008 and 2009 to 2010. In 2007 to 2008 (**Figure 5**, upper panel), only two grid squares with significantly high rates were seen one at the extreme east of the site (10.41 deaths/1000 person-years, PY), the other towards the west (563.23 deaths/1000 PY). The latter was in a square with a very low population

and thus likely to be a statistical outlier. Grid squares with significantly low standardised adult HIV/TB mortality rates were predominantly in the southern and western areas of the site with two additional squares located to the north of the Bhubezi health community health centre (Bhubezi).

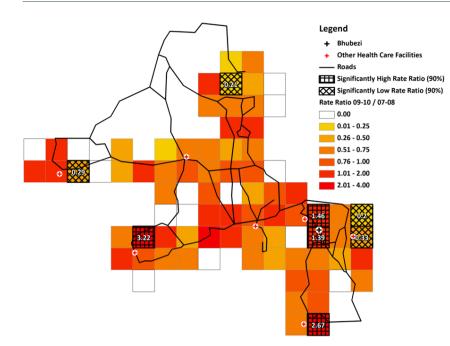
In 2009 to 2010 (Figure 5, lower panel) there were 4 grid squares with significantly low rates in the eastern region of the site in the area around Bhubezi. Other low rate grid squares were identified towards the west and north of the site. There were two grid squares with significantly high HIV/TB mortality rates one containing Bhubezi (8.23 deaths/1000 PY) and the other towards the southwest of the site (15.76 deaths/1000 PY)

The rate ratio plot (Figure 6) shows four grid squares with significantly high rate ratios indicating an increase in the adult HIV/TB mortality rates between the two periods. One was located in the square containing Bhubezi (rate ratio = 1.39) and another directly to the north (rate ratio = 1.46), another was in the extreme south of the site (rate ratio = 2.67) and one towards the west (rate ratio = 3.22). Of the four grid squares with significantly low rate ratios, two were located to the east of Bhubezi. The rate ratios for these two squares are 0.20 and 0.33, indicating

decreases of 80% and 67% respectively in the adult HIV/ TB mortality rates in these regions. Other grid squares with low mortality rate ratios were seen in the north and west of the site.

The Moran's I value for the HIV/TB mortality rate ratios was –0.03 indicating the spatial distribution of changes in HIV/TB mortality rates was essentially random with no evidence for global spatial correlation.

Non–HIV/TB mortality. For adult deaths other than those caused by HIV related disease or TB, in the period 2007 to 2008, two grid squares with significantly high mortality rates were identified towards the north of the site and one in the south (see Figure S1 in Online Supplementary Document). In contrast, low rate grid squares were mainly found in the eastern, western and central areas of the site. In 2009 to 2010 the four grid squares showing significantly high rates were located in the eastern, southern and central re-



For the deaths due to causes other than HIV/TB, two low risk clusters were identified (4 & 5) over the same time period, October 2010 to December 2010. Cluster 4 (P=0.05) covers a large area of the west and central region of the site, whilst cluster 5 with a low level of statistical significance (P=0.18) covers a slightly smaller area towards the east of the site.

DISCUSSION

In this study three complementary techniques were used to investigate the changes in the geographical patterns of cause specific adult mortality over a period in which ART was rolled out and a community health centre opened in a rural South African community.

There was a 30% decrease in adult HIV/

TB mortality between 2007 to 2008 and 2009 to 2010. However, for one community, village Q, there was a 35% increase in the adult HIV/TB mortality rate over the same period. As the rates were age and gender standardised, other factors must explain these differences. Village Q was originally established to provide homes for Mozambican refugees, this suggested that the ethnic profile of the village might be an important factor in determining the take-up of ART and subsequent decrease in mortality. However in our study we also found that in other predominantly Mozambican communities, such as villages L, R, S and T, there were decreases in the HIV/TB mortality rate over the same period. Hence ethnicity alone cannot explain the mortality changes. Furthermore, village L neighbours village Q, highlighting the geographical heterogeneity in the epidemic trajectories seen for closely neighbouring communities. This heterogeneity in rates between villages is consistent with patterns in all cause mortality identified between 1992 and 2007 [36] in this area.

The inverse relationship between the adult mortality rate ratio and the baseline adult HIV/TB mortality rate suggests that at a population level the impact of ART was greatest in the communities where the need was greatest. It is possible the higher HIV/TB mortality rates in some communities increased the awareness of the disease and hence the likelihood of individuals in those areas getting tested and starting treatment. Further qualitative studies would be needed to confirm whether this was the case.

There was no evidence of overall changes in adult mortality rates due to causes other than HIV related disease and pulmonary TB between the two time periods. This suggests that the reduction in HIV/TB mortality was explained by the provision of ART, rather than a general improvement

Figure 6. HIV/TB mortality rate ratios for 2009–2010 compared to 2007–2008 for the Agincourt HDSS site. For grid squares with significantly low rate ratios, the upper bound of the 90% confidence interval is less than the mean rate ratio. For grid squares with significantly high ratios, the lower bound of the 90% confidence interval is greater than the mean rate ratio. The label is the mortality rate ratio for the grid square.

gions of the site. There were eight grid squares with significantly low rates. These were distributed throughout the site other than in the extreme southern and western areas.

Two grid squares had significantly high rate ratio values, one just below Bhubezi (rate ratio = 2.23) and one towards the centre of the site (rate ratio = 1.92). Five grid squares showed significantly low rate ratios, one was just to the north-east of Bhubezi the others towards the centre of the site.

The Moran's I value for the non–HIV/TB rate ratios was –0.02 indicating the spatial variation in non–HIV/TB mortality rate changes was essentially random again showing no evidence for global spatial correlation.

Spatio-temporal clustering

For HIV/TB mortality two low risk clusters (1 & 2) and 1 high risk cluster (3) were identified as shown in Figure 7. Cluster 1 (P=0.04) was located in the centre of the site the time period was from August to December of 2010. Cluster 2 (P=0.03) to the southeast of Cluster 1 was between November 2007 and September 2008. Cluster 3 had a lower level of statistical significance (P=0.12), its time period from June 2007 to May 2008 partially overlapped that for cluster 2. It was located in the lower southeast region of the site.

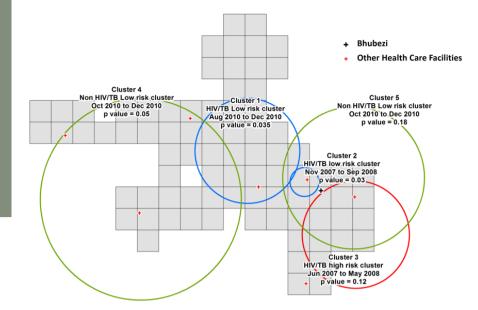


Figure 7. Spatio–temporal clusters with significantly raised or lowered rates of deaths due to HIV/TB and Non HIV/TB over the period 1 Jan 2007 to 31 Dec 2010.

in other aspects of health care provision in the area. However we do see highly heterogeneous patterns of change between different communities. Also the patterns of change in mortality rates differ markedly for the two categories of cause of death. An example of this is seen for village O which had a 37% increase in non–HIV/TB mortality and a 34% decrease in HIV/TB mortality, between

The analysis by grid square further emphasises the pattern of local heterogeneity and shows how this can also be seen at a sub–village level. As an example, the four populated grid squares located towards the extreme west of the site in the map of adult HIV/TB mortality (Figure 6) are subsections of the same village. Three have increased HIV/TB mortality rates whilst the fourth shows a reduction of 71% between the earlier and later time periods. It is possible that the characteristics of the different sub–regions of the village are influenced by those of neighbouring communities.

The existence of clusters of high and low HIV/TB mortality towards the east of the study site (Figure 7) also shows the local heterogeneity in the risk of death related to these conditions. In comparison, a study looking at infant HIV/ TB deaths in the site between 2000 and 2005 identified high mortality risk hot spots in the central, south–eastern and south–western areas [37]. This analysis shows different geographical locations for the high and low risk clusters of mortality attributable to different causes consistent with a previous study of adult mortality patterns in the site from 1993–2010 [38].

Visual analysis showed no evidence for lower HIV/TB rate ratios in areas close to the clinics providing ART. A study in

a rural area of KwaZulu–Natal in South Africa showed that ART uptake was inversely related to the distance individuals lived from the clinic providing treatment [39]. Previous studies in this site did identify associations between the mortality risk and the straight-line distance between an individual's residence and local clinics [40,41].

These patterns have important implications for those planning new health facilities or initiating community– based health interventions. Whilst it is important that the physical barriers to access are reduced, for example by locating new health centres in order to obtain the greatest reduction in travel times for the population which is

served [31], consideration should also be made to the different morbidity patterns across the community. Furthermore as we see from the patterns of HIV/TB rate ratios in Figure 6 different areas within a short distance of the Bhubezi health centre saw very different epidemic trajectories over the period of the study. This suggests that to have an effective impact, the various barriers to access experienced by different sub-sections of the community, must be addressed [42]. Clearly there are issues of temporality in such an approach as we are making assumptions about levels of current illness based on past mortality levels. Also knowing the place of residence of an individual at the time of their death does not necessarily tell you where the person was exposed to the risk factors leading to death. This is especially important in an area like this where we see significant numbers of individuals returning from urban areas when their illness has progressed such that they are no longer able to maintain employment and live independently [43].

A potential limitation in this analysis is the rather high level of indeterminate causes of death. However there is no evidence that the indeterminate data introduced a spatial bias. The preponderance of indeterminate causes among younger individuals and males probably reflects patterns of temporary migration, with a number of those deaths occurring away from home and hence difficult to follow-up by verbal autopsy. As there was a slightly higher proportion of deaths for which no cause could be defined in 2009-2010 compared to 2007-2008 (16.3% vs 15.7%) we can assume that the cause specific mortality ratios are a slight underestimate. Also as relatively short time windows were used to accumulate the data, the numbers of deaths accrued was relatively low compared to previous studies [36] leading to relatively wide confidence intervals for the rates and rate ratios calculated.

CONCLUSIONS

The patterns that emerge from this study are complex. In some areas there appears to be a high level of intra-village coherence with individual villages showing distinct mortality characteristics which differ from those of neighbouring villages. In others the pattern is less clear. This work confirms the conclusions made by other studies in the region that identified heterogeneous pattern of micro-epidemics within a more generalised epidemic [10–12,14,17]. Our results confirm trends shown by Tanser and colleagues [8] of considerable local geographic variation in HIV prevalence in a rural area of Kwa Zulu Natal South Africa. However spatial patterns of HIV related mortality will be affected by both the distributions of risk factors for infection and local availability of testing and treatment. In our case there are no obvious associations with the location of major roads crossing the site. This study shows that a micro-level analysis may be useful in mounting an appropriate public health response to HIV in a local area. In a further study, currently being prepared for publication, we assess the influence of various risk factors which may explain the spatial patterns that have been identified. Conclusions drawn from a spatial analysis such as is presented here can be used as a starting point for investigations of factors influencing the differing current morbidity patterns seen in different communities.

Geo–located cause specific mortality data as used in this analysis is often lacking in resource poor regions [44]. However a mobile phone based application which can be used to collect verbal autopsy data and assign causes of death, as well as automatically registering GPS coordinates, is now available [45]. This gives the potential in the future for a greater geographic coverage of mortality data beyond the existing limited number of research sites for which it is available.

UNAIDS and others have emphasised that in deciding how to respond to HIV one must "Know your epidemic" [46]. This study emphasises the importance of that approach.

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"SaTScan™ is a trademark of Martin Kulldorff. The SaTScan™ software was developed under the joint auspices of (i) Martin Kulldorff, (ii) the National Cancer Institute, and (iii) Farzad Mostashari at the New York City Department of Health and Mental Hygiene."

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Ethical approval: Ethical clearance for the data collection for this study was given by the University of the Witwatersrand Human Research Ethics Committee (Medical). Clearance Certificates M960720 and M110138 'Investigating and Responding to Changes in the Health and Population Dynamics of Rural South Africans'. Verbal consent was obtained from the respondent prior to every follow–up survey.

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Urbanization and prevalence of type 2 diabetes in Southern Asia: A systematic analysis

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Dr Kit Yee Chan Centre for Population Health Sciences The University of Edinburgh Medical School Teviot Place Edinburgh, EH8 9AG Scotland, UK k.chan@ed.ac.uk **Background** Diabetes mellitus is one of the diseases considered to be the main constituents of the global non–communicable disease (NCD) pandemic. Despite the large impact that NCDs are predicted to have, particularly in developing countries, estimates of disease burden are sparse and inconsistent. This systematic review transparently estimates prevalence of type 2 diabetes mellitus in Southern Asia, its association with urbanization and provides insight into the policy challenges facing the region.

Methods The databases Medline and PubMed were searched for population–based studies providing estimates of diabetes prevalence in the Southern Asia region. Studies using WHO diagnostic criteria of fasting plasma glucose (FPG) \geq 7.0mmol/L and/or 2-hour plasma glucose (2hPG) \geq 11.1mmol/L were included. Data from eligible studies was extracted into bubble graphs, and trend lines were applied to UNPD figures to estimate age–specific prevalence in the regional population. Estimates specific to sex, area of residency, and diagnostic method were compared and trends analysed.

Results A total of 151 age–specific prevalence estimates were extracted from 39 studies. Diabetes prevalence was estimated to be 7.47% for 2005 and 7.60% for 2010. Prevalence was strongly associated with increased age, male gender and urban residency (P<0.001).

Conclusion Diabetes prevalence in Southern Asia is high and predicted to increase in the future as life expectancy rises and the region continues to urbanise. Countries in this region need to improve NCD surveillance and monitoring so policies can be informed with the best evidence. Programs for prevention need to be put in place, and health system capacity and access needs to be assessed and increased to deal with the predicted rise in NCD prevalence.

In recent years the issue of non–communicable diseases (NCDs) has been identified as a pressing concern that has come to the forefront of international policy discussion. NCDs are the leading causes of death and disability worldwide [1]. It was estimated that 33 million deaths in 2008 occurred from NCDs, accounting for almost two–thirds of all deaths for that year [2]. In addition, estimates suggest that these may increase further to a projected 52 million deaths by 2030, nearly five times as many deaths as projected for communicable diseases [3]. Type 2 diabetes mellitus (DM),

along with cardiovascular disease, cancers, and chronic respiratory diseases, are considered four primary constituent diseases of the global NCD pandemic [3,4]. Importantly, the main risk factors for these diseases are modifiable and these diseases are heavily influenced by lifestyle and behaviour [5]. Shared risk factors between these diseases - such as eating an unhealthy diet high in saturated fat and sugar, a lack of physical activity, and tobacco smoking - account for over two-thirds of new NCD cases and increase the risk of exacerbations in those who already have these diseases [5]. These risk factors and resulting diseases are not limited to high-income countries - a disproportionate NCD burden is borne by developing countries. Over 80% of diabetes and cardiovascular deaths worldwide occur in low- and middle-income countries (LMICs), and many of the risk factors for these NCDs are associated with the country development process through globalisation and urbanisation [3]. The prevalence of the common NCDs increases with advancing age, so as life expectancy in LMICs increases the burden of NCDs is also expected to rise.

Non-communicable diseases are more likely to affect people who are socioeconomically disadvantaged, furthering health inequalities [6]. This can be due to contextual factors relating to the society and place in which people live in addition to behavioural factors. In LMICs, diabetes and its risk factors are associated with lower education levels [3]. The higher burden of NCDs poses additional problems for populations of developing countries that have lower levels of educational achievement and income. Limited health care capacities and lack of social protection for large parts of the population mean that treatment and support for NCDs is often unavailable or catastrophically expensive [5,7]. In addition, NCDs have significant socioeconomic effects. Nearly a third of NCD deaths in LMICs occur below the age of 60 [1]. These deaths at economically and socially productive ages have much wider consequences for these developing countries, with the loss of productivity and health system expenditure becoming major barriers for national economic development and progress [5,8]. On individual or household levels, the sustained nature of NCDs and resulting disabilities can lead to difficulties in working or seeking employment. Additionally, the long-term care that NCDs require and the high cost of health care in many developing countries have major impacts on household income, potentially leading to vicious cycles of poverty and illness [5]. The overall economic cost of NCDs cannot be understated: in India in 2004-2005, NCD health care expenditure and total income lost due to these diseases was estimated to amount to 1% of its massive economy [3].

Despite the serious implications of the global NCD burden, it is only recently that determined policy action has been seen. The UN High–Level Meeting on NCDs in 2011 led the way for an international response, providing guidance on how to integrate NCD prevention and control across sectors and at all levels of government [1,3]. Furthermore, monitoring and surveillance capabilities of several highburden countries have shown an increased capacity in recent years [2]. However, many of the recommended changes – such as health care system reform towards sustainable universal care, and integration of NCD prevention into multi-sectoral responses - may take several years to implement, particularly in the LMICs that bear the brunt of the global NCD burden. Meanwhile it is essential that these regions have reliable estimates of NCD burden to inform policy decisions with relevant evidence and help set appropriate health care and research priorities [9]. Transparent, up-to-date estimates of NCD burden allow monitoring of the diseases as well as evaluation of current policies, and are vital tools for planning policies and interventions to tackle the global NCD pandemic. This paper will attempt to address part of this need by carrying out a systematic literature review to estimate the prevalence of type 2 DM in Southern Asia.

Box 1 briefly reviews approaches to diagnosis and known risk factors for type 2 diabetes [10-18]. Table 1 displays current WHO diagnostic criteria for venous plasma for fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT). Diagnosis can be made through the use of either test alone or together. Specific values for capillary measurements and whole blood have been provided in previous WHO publications as well [12]. In terms of geographic focus of this study, the UN's Southern Asia region is comprised of nine countries [19]. General information regarding each country is given in Table 2, sourced from the World Bank online database [20]. The majority of Southern Asian countries are low or low-middle income countries [20]. The total population of the Southern Asia region comprises approximately 25% of the world total population [20]. India was estimated to have the highest number of diabetic adults in 2000 [21] and 2010 [22], and both these studies predicted it would continue to have the highest number of diabetic adults by 2030. Pakistan and Bangladesh were both estimated to be in the top ten as well. As such, an estimate of the diabetes prevalence for this region would provide a major insight into the global picture of diabetes burden.

This paper aims: (i) to contribute to the evidence base on type 2 diabetes mellitus in Southern Asia by systematically reviewing the relevant literature; (ii) to compare the prevalence estimates provided through different methods of diagnosing type 2 diabetes mellitus; (iii) to provide an assessment of the role of urbanization on the burden of Type 2 diabetes mellitus in the UN Southern Asia region based on the best available evidence; and (iv) to discuss the significance of the regional estimate and the implications it may have on public health policy.

Box 1 Type 2 diabetes – diagnosis and risk factors

Type 2 diabetes mellitus (DM) is a metabolic disease characterised by persistent hyperglycaemia and disturbed carbohydrate, protein, and fat metabolism. It may present with combinations of typical symptoms such as polydipsia (increased thirst), polyphagia (excessive hunger), polyuria (increased passage of urine), glycosuria (glucose in urine), lethargy, and weight loss. These symptoms reflect the underlying DM pathophysiology of peripheral insulin resistance combined with inadequate pancreatic insulin secretion [10]. Many diabetic patients may be asymptomatic but in the long term uncontrolled hyperglycaemia can lead to severe complications such as diabetic retinopathy, neuropathy and nephropathy. Type 2 DM can be diagnosed through biochemical measurements even if there are no presenting symptoms [11].

Under World Health Organisation (WHO) guidelines, there are currently two main diagnostic tests used to diagnose DM – the Fasting Plasma Glucose (FPG) test and the Oral Glucose Tolerance Test (OGTT) [11]. FPG involves measuring the level of glucose in a fasting (.8 hours without food) patient's blood, often after an overnight fast. OGTT is also carried out on fasting patients and involves measurement of baseline blood glucose, followed by ingestion of 75g anhydrous glucose, and a subsequent blood glucose measurement after two hours to determine the efficacy with which glucose has been eliminated from the patient's blood [12]. Although WHO has also recently advocated the measurement of glycatedhaemoglobin (HbA1_c) for diagnostic purposes [13], the stringent quality assurance tests required for its effective usage have limited its use in epidemiological studies to date. Additional notes on these diagnostic methods are provided in **Online Supplementary Document**.

The aetiology of type 2 DM is complex and likely involves a host of different factors, many of which are not fully understood. Common risk factors in the general population include older age, being overweight or obese, hypertension, leading an inactive lifestyle, smoking, and consuming an energy–dense diet [14,15]. Several of these risk factors may be considered 'lifestyle' factors that are potentially modifiable. However, a strong genetic component is also implicated in Type 2 DM, with relatives of diabetics at increased risk of developing it themselves, and certain ethnic populations believed to have increased susceptibility to diabetes [16,17]. South Asians in particular have been found to possess adverse body fat patterning that that may predispose to insulin resistance [18], and have higher diabetes risk than Caucasians with equivalent body mass indices (BMI) [16]. This non–modifiable genetic susceptibility for South Asians means it is of even greater importance that policies address modifiable risk factors in order to tackle burgeoning diabetes prevalence in the region.

Table 1. World Health Organization's 2006 diagnostic criteriafor type 2 diabetes

Fasting plasma glucose (FPG) \geq 7.0mmol/L (126mg/dl) and / or

2-hour plasma glucose (OGTT 2hPG) ≥11.1mmol/L (200mg/dl)

FPG –fasting plasma glucose, OGTT –oral glucose tolerance test.

METHODS

A systematic literature search of published studies providing population–based prevalence estimates of type 2 diabetes mellitus in Southern Asia was carried out. The online databases Medline and PubMed were searched, using the OVID search form for the Medline database and the default search engine for PubMed. Search terms for Medline and PubMed are given in Table 3 and Table 4 respectively. Both Medical Subject Headings (MeSH terms) and keywords were used for the Medline search. The Medline search was more focused due to OVID's Advanced Search feature, while the PubMed search was left broader in order to pick up a larger selection of studies. The final searches were carried out on 13 February 2013. Box 2 shows inclusion criteria, exclusion criteria and quality evaluation criteria.

Study selection

The literature search of online databases resulted in a total of 5653 studies: 1754 from Medline and 3899 from PubMed. After initial analysis of titles and abstracts, 402 studies were selected that matched inclusion and exclusion criteria. 51 duplicate studies were removed and full texts

Table 2. Sout	hern Asia cou	untries – seleo	cted characte	eristics

Table Li Sourie	in rista countries	selected characteristic	5			
COUNTRY	Population, ×1000 (2011)	Life expectancy at birth (2010)	GNI per capita (US\$) (2011)	GDP US\$ growth, % (2011)	Total expenditure on health (% GDP) (2011)	Physicians per 1000 population (2011)
Afghanistan	35320	48	1140	+6%	9.6	0.210
Bangladesh	150394	69	940	+7%	3.7	0.295
Bhutan	738	67	5570	+6%	4.1	0.023
India	1241492	65	3590	+7%	3.9	0.649
Iran	74799	73	11420†	+2%†	5.8*	0.890
Maldives	320	77	7430	+7%	8.5	1.595
Nepal	30486	68	1260	+4%	5.4	0.210†
Pakistan	176745	65	2870	+3%	2.5	0.813
Sri Lanka	20869	75	5520	+8%	3.4	0.492

GNI - gross national income, GDP - gross domestic product

*Data from 2009, most recent available data but likely inaccurate following punitive economic sanctions. †Data from 2004.

Table 3. OVID Medline search terms

IGDI	So ovid medine search terms	
SEAR	CH TERMS	No. of studies
1	Diabetes Mellitus, type 2/	74709
2	"adult–onset diabetes".tw	358
3	(diabetes adj2 type 2).tw	54707
4	"non-insulin dependent diabetes".tw	8297
5	NIDDM.tw	6732
6	Diabetes Mellitus/ or Diabetes Mellitus, type 2/	155830
7	1 OR 2 OR 3 OR 4 OR 5 OR 6	173525
8	exp morbidity/ or exp mortality/	563526
9	incidence.tw	464724
10	(prevalen* or mortality or epidemiol*).tw	961 509
_11	Épidemiology/	11218
12	"cost of illness"/	15625
_13	(burden adj2 diseas*).tw	7633
_14	8 OR 9 OR 10 OR 11 OR 12 OR 13	1586465
15	Bangladesh/ or Bhutan/ or India/ or Afghanistan/ or Iran/ or Nepal/ or Pakistan/ or "Sri Lanka"/	102952
16	Indian Ocean Islands/	568
17	(afghan* or bangladesh* or bengal* or bhutan* or iran* or india* or nepal* or pakistan* or maldiv* or srilanka *).tw	122321
_18	15 OR 16 OR 17	161040
19	7 AND 14 AND 18	1896
_20	Limit 19 to (humans and yr="1980–Current")	1754 results

Box 2 Literature search: Inclusion criteria, exclusion criteria and quality evaluation criteria

Inclusion criteria:

- Population– or community–based study in a Southern Asian country providing prevalence estimates of type 2 diabetes mellitus based on primary data.
- All published study designs and all languages.
- Studies post–1980 with ≥200 participants.
- Studies looking at adults (≥ 20 years).
- Studies diagnosing diabetes through biochemical measurements.

Exclusion criteria:

- Studies investigating other forms of diabetes, such as gestational diabetes or diabetes insipidus.
- Hospital- or clinic-based studies.
- Studies diagnosing diabetes through self-reported questionnaires or symptoms only.
- Study populations specifically predisposed to diabetes, such as relatives of known diabetics.
- Studies investigating prevalence of complications in a diabetic cohort without commenting on actual prevalence of diabetes in area or community.

Quality evaluation criteria:

- Diabetes diagnosed through fasting plasma glucose (FPG) after ≥8 hours fasting, and/or oral glucose tolerance test (OGTT) two hours after ingestion of 75g anhydrous glucose or equivalent.
- Appropriate diagnostic criteria for diabetes most recent WHO recommendations of FPG≥7.0mmol/L and/or 2hPG≥11.1mmol/L for venous plasma, or equivalent for other sample types. Stated whether blood samples were venous or capillary, and whether whole blood or plasma was analysed.
- Clearly defined population recruited through representative sampling methods.
- Description of how known diabetics were accounted for.

Table 4. PubMed search terms

Search terms	No. studies
Diabetes AND (Afghanistan OR Bangladesh OR	3899 results
Bhutan OR India OR Iran OR Maldives OR Nepal	
OR Pakistan OR Sri Lanka) AND (Epidemiology	
OR Incidence OR Prevalence OR Mortality)	

of the remaining 351 studies were further analysed and quality assessed. 39 studies were included in the final analysis, including 2 papers identified through reference lists of other assessed studies. A visual summary of the study selection process is presented in Figure 1.

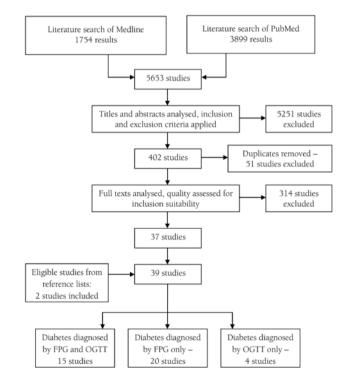


Figure 1. Study selection process. FPG –fasting plasma glucose, OGTT –oral glucose tolerance test.

Data extraction

Titles and abstracts of all studies obtained through the database searches were evaluated. Inclusion and exclusion criteria were applied. Basic details of all studies such as title, authors, country, study year, year of publication, and sample size were extracted into an Excel spreadsheet for ease of full text evaluation. After initial extraction, full texts of the studies were analysed and assessed for quality criteria. Quality assessment information is presented in Online Supplementary Document. Studies for which full text was not available were requested through inter-library loans. Duplicate studies were identified through study locations and matching sample sizes, and were removed. In addition, the reference lists of the selected studies were examined for relevant papers not captured by the literature search. These new studies were subsequently evaluated and added to the spreadsheet.

Another Excel spreadsheet was created for eligible studies selected through full text analysis. All the above data was extracted in addition to data on method of diagnosis; diagnostic criteria; specific location of the study; whether the study described the surveyed area as urban, rural, mixed or none; age range of participants and mean age if provided; diabetes prevalence in sample; and sex-specific sample size, mean age, and diabetes prevalence. Many studies looked at several different cohorts in various areas, often for purpose of comparison. These multiple cohorts were recorded separately so that individual sample characteristics could be differentiated. Three separate sheets were created for studies depending on their method of diagnosing new diabetes: one for studies that diagnosed diabetes on the basis of both FPG and OGTT results; one for studies using only FPG results; and one for studies using only OGTT results. These spreadsheets were the basis for prevalence estimation.

Data analysis

To allow for comparison between studies, all reported prevalence estimates were converted to prevalence/1000 population through the equation:

Prevalence = Number of diabetes cases ×1000 / Sample size

During data modelling, the mean age, sample size, and age–specific prevalence estimates (per 1000 population) of all selected studies were used to create bubble graphs representing the data. If this information was missing for particular cohorts, it was calculated from the data that was available, as detailed in **Online Supplementary Document**. Several bubble graphs were created: for overall prevalence, sex–specific prevalence, urban/rural prevalence, and prevalence for specific diagnostic methods.

In order to calculate population prevalence estimates for the region, trend lines with the power function were com-

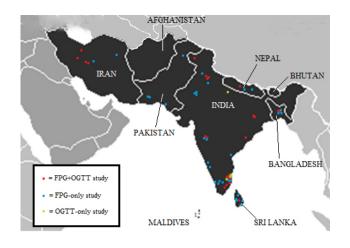


Figure 2. Approximate geographic locations of the study cohorts. FPG –fasting plasma glucose, OGTT –oral glucose tolerance test.

puted from the graphs to represent the relationship between age and prevalence for the selected data set. These were chosen because they had the highest r-squared (R^2) values for these graphs and therefore accounted for the highest fraction of variance in the data. Statistical significance (p-values) of differences observed through any comparisons was derived directly from the model. The resulting equations for overall combined prevalence, total male prevalence and total female prevalence were applied to 2005 UNPD population estimates, the closest to the median study year of 2006 [23]. Prevalence results were multiplied by population figures for each age group, thereby giving an estimate of the total number of expected diabetes cases for each one. Totalling these up and taking a percentage of the total adult population allowed calculation of overall diabetes prevalence, for each sex separately and combined.

Study characteristics

Of the 39 studies included in the analysis, 15 studies diagnosed diabetes using both FPG and OGTT methods, 20 solely using FPG, and 4 studies using OGTT only. Several studies looked at more than one cohort when estimating diabetes prevalence, often for purposes of comparison. A total of 57 cohorts were investigated by the 39 studies (Figure 2). During analysis each different cohort was represented independently. Within these cohorts, age–specific prevalence estimates were represented individually if available. Table 5 provides an overview of study characteristics by country. Population estimates are based on 2005 UNPD data [23].

The country with the largest number of studies, of all types, was by far India. It was also the only country for which suitable OGTT–only studies were available. No suitable studies of any kind were found in the literature search for

Country	Proportion of regional adult (≥ 20) population (%)	No. of FPG & OGTT combined studies	No. of FPG —only studies	No. of OGTT —only studies	Total No. of studies
Afghanistan	1.28	0	0	0	0
Bangladesh	8.65	2	2	0	4
Bhutan	0.04	0	0	0	0
India	73.24	9	8	4	21
Iran	4.78	2	2	0	4
Maldives	0.02	0	0	0	0
Nepal	1.53	1	2	0	3
Pakistan	8.97	0	4	0	4
Sri Lanka	1.49	1	2	0	3
Total	100.00	15	20	4	39

Table 5. Study characteristics by country

FPG - fasting plasma glucose, OGTT - oral glucose tolerance test

three countries: Afghanistan, Bhutan, and the Maldives. The remaining five countries had a mixture of FPG–only and FPG+OGTT combined studies, with the exception of Pakistan, for which only FPG studies were found. The mean study size was 5178, with samples ranging from 331 to 25969 participants. The median study year based on provided information was 2006 – while the earliest publication year was 1992, the earliest specified study year was 1998 and the most recent study year was 2009. More information about the study cohorts is given in Table 6 and Table 7, and additional information is provided in **Online Supplementary Document**.

RESULTS

Figure 3 displays the relationship between mean age of sample and overall diabetes prevalence (both sexes combined, all diagnostic methods). A total of 151 individual

		,	,	
Country	No. of FPG & OGTT combined		No. of OGTT—only	Total No. of cohorts
	COHORTS		COHORTS	
Afghanistan	0	0	0	0
Bangladesh	2	3	0	5
Bhutan	0	0	0	0
India	20	9	6	35
Iran	2	2	0	4
Maldives	0	0	0	0
Nepal	1	2	0	3
Pakistan	0	4	0	4
Sri Lanka	1	5	0	6
Total	26	25	6	57

Table 6. Cohort cl	naracteristics h	by country
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FPG - fasting plasma glucose, OGTT - oral glucose tolerance test

Table 7. General cohort characteristics

Characteristic	FPG & OGTT Combined Cohorts	FPG—only cohorts	OGTT —only cohorts	Total
Rural	9	13	3	25
Urban	15	7	3	25
Both/None	2	5	0	7
Minimum size	526	331	588	
Maximum size	12514	25969	1213	
Mean size	3580	4126	954	

FPG - fasting plasma glucose, OGTT - oral glucose tolerance test

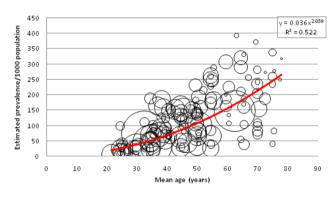


Figure 3. The relationship between crude prevalence of type 2 diabetes in Southern Asia and age.

data points for age-specific prevalence were plotted from 57 cohorts. 65 individual points were available from FPG and OGTT combined studies, 77 from FPG-only studies, and 9 from OGTT-only studies (Tables 8, 9 and 10). Age-specific prevalence data are provided in Online Supplementary Document. Figure 3 shows a positive association between mean age and diabetes prevalence. Table 11 illustrates this association using the trend line equation derived from overall prevalence results and also displays population prevalence estimates based on 2005 UNPD estimates for the Southern Asia region. Based on these figures, the diabetes population prevalence for 2005 was estimated to be 7.47%. The 50-54 age group had the highest proportion of the burden at 11.31%, and the 20-24 group had the lowest proportion of the burden at 4.64%. A total of 51.3% of the burden was seen in those aged 50 or more. The diabetes burden increases with age until the ages of 50 and 54, after which it decreases. This is due to the population age structure in 2005 -diabetes prevalence per 1000 population is shown to increase continuously with age.

Table 12 shows the overall prevalence equation applied to 2010 UNPD population estimates, and Figure 4 compares the estimated numbers of diabetics between 2005 and 2010. A higher overall prevalence estimate is observed for

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Table 8. Individual study prevalence data: EPG+OGTT combined studies

Authors	Country	Urban/	STUDY	Age	Mean	Overall	Male	Mean	Size of	Female	Mean	Size of
Autions	COOMINI	RURAL	SAMPLE	RANGE OF	AGE	DIABETES	DIABETES	AGE	GROUP	DIABETES	AGE	GROUP
		NUNAL	SIZE	PARTICI-	AUL	PREVALENCE	PREVALENCE	AUL	diloor	PREVALENCE	AUL	anoor
			OILL	PANTS		(/1000	(/1000			(/1000		
						POPULATION)	MEN)			WOMEN)		
Bhowmik et al (2012) [24]	Bangladesh	Rural	2293	≥20	50	79	90	43.9	842	71	40.4	1451
Rahim et al (2008) [25]	Bangladesh	Rural	3954	≥20	37.1	70	75	39	1592	67	35.9	2375
Nazir et al (2012) [26]	India	Urban	2188	≥20	38.7	158	_	_	-	_	_	-
Prasad et al (2012) [27]	India	Urban	1178	20-80	45.6	157	178	47	590	138	44.2	588
Anjana et al (2011) [28]	India	Urban	1029	≥20	50*	137	_	_	-	_	_	-
		Rural	2480	≥20	50*	78	_	_	_	_	_	_
		Urban	1093	≥20	50*	109	_	_	_	—	_	_
		Rural	2476	≥20	50*	65	—	_	_	—	_	-
		Urban	840	≥20	50*	135	_	—	-	_	-	-
		Rural	2051	≥20	50*	30	_	_	-	-	-	
		Urban	839	≥20	50*	142	_	_	-	_	-	
		Rural	2247	≥20	50*	83	-	_	_	-	_	_
Deepa et al (2011) [29]	India	Urban	526	≥20	47.8	154	-	_	_	-	-	_
		Urban	596	≥20	41.1	153	-	_	_	-	-	_
Ravikumar et al (2011) [30]	India	Urban	2227	≥20	42.7	157	-	_	_	-	_	_
Ramachandran et al (2008) [31]	India	Urban	2192	≥20	38.2	186	209	38.2†	1053	167	38.2†	1139
		Urban	2290	≥20	36.8	164	171	36.8†	988	159	36.8†	1302
		Rural	2584	≥20	38	92	104	38.0†	1280	80	38.0†	1304
Zargar et al (2008) [32]	India	Rural	3024	20-40	30.8	25	-	_	_	-	-	
Sadikot et al (2004) [33]	India	Urban	10617	≥25	44.8	59	56	44.5	5379	58	45.1	5238
		Rural	7746	≥25	44.2	25	25	44.1	3629	25	44.3	4117
Ramachandran et al (2001) [34]	India	Urban	11216	≥20	42.7	139	138	42.4	5288	140	43.0	5928
Hadaegh et al (2008) [35]	Iran	Urban	9489	≥20	43.5	142	141	44.8	4006	143	42.4	5483
Sadeghi et al (2007) [36]	Iran	Both	12514	≥19	39	63	54	39†	6123	71	39†	6391
Shrestha et al (2006) [37]	Nepal	Urban	1012	≥40	54.7	191	246	54.9‡	423	151	54.5‡	589
Katulanda et al (2008) [38]	Sri Lanka	Both	4388	≥18	46.1	126	98	46.3	1720	109	46	2668

FPG – fasting plasma glucose, OGTT – oral glucose tolerance test *Estimated mean age based on hypothetical maximum age of 80. †Sex–specific mean ages not provided, overall mean age used for both sexes.

‡Estimated mean age based on age-group breakdowns.

Table 9. Individual study prevalence data: FPG–only studies

Authors	Country	Urban/ Rural	Study sample size	AGE Range of Partici-	MEAN AGE	Overall Diabetes prevalence	Male diabetes prevalence	Mean age	Size of group	Female diabetes prevalence	Mean age	Size of group
				PANTS		(/ 1000 population)	(/1000 men)			(/ 1000 women)		
Rahman et al (2007) [39]	Bangladesh	Rural	975	≥20	38.9	85	94	41.7	360	80	37.3	615
Hussain et al (2005) [40]	Bangladesh	Rural	4757	≥20	37.5	23	19	39.7†	2030	25	35.8*	2720
		Urban	1555	≥20	33.5	81	77	35.9*	731	85	31.4*	824
Pandey et al (2013) [41]	India	Rural	2616	35–70	46.7	43	-	-	_	-	-	-
		Urban	2008	35–70	48.4	151	-	-	_	_	_	_
Vaz et al (2011) [42]	India	Rural	1266	≥20	39	103	84	39†	609	120	39†	657
Rao et al (2010) [43]	India	Rural	1239	≥30	51.3	160	188	50	434	144	52	805
Vijayakumar et al (2009) [44]	India	Rural	1645	≥18	47.2	146	165	48.2	624	135	46.2	1021
Namperumalsamy et al (2009) [45]	India	Both	25969	≥30	47	108	-	_	_	_	_	-
Chow et al (2006) [46]	India	Rural	4538	≥30	46.8	132	-	_	_	-	-	_
Gupta et al (2003) [47]	India	Both	1091	≥20	43.9	123	132	43.3	532	115	44.4	559
Misra et al (2001) [48]	India	Urban	532	≥ 18	35.4	103	112	37.8	170	99	34.3	362
Esteghamati et al (2009) [49]	Iran	Both	3397	25–64	44.2	87	_	_	_	-	-	-
Azimi–Nezhad et al (2008) [50]	Iran	Both	3438	20–64	48.5	55	-	_	_	_	_	-
Sharma et al (2011) [51]	Nepal	Both	14008	≥20	41.4	63	81	41.4†	5326	53	41.4†	8682
Paudyal et al (2008) [52]	Nepal	Rural	1475	≥40	54.7	41	_	_	_	_	_	_
Basit et al (2011) [53]	Pakistan	Rural	1264	≥25	42.3	142	165	43.5	424	131	41.7	840
Zafar et al (2011) [54]	Pakistan	Urban	1091	12-80	36	131	154	36†	293	123	36†	798
Mahar et al (2010) [55]	Pakistan	Urban	19211	30–90	42	87	_	_	-	-	-	-
Basit et al (2002) [56]	Pakistan	Rural	2032	≥25	38.9	72	119	40.4	670	49	38.1	1362
Pinidiyapathirage et al (2013) [57]	Sri Lanka	Urban	2986	35–64	52.3	247	233	52.2†	1349	259	52.3†	1637
Wijewardene et al (2005) [58]		Urban	4301	30–65	46.8	175	183	46.4	1891	168	47.2	2410
Sri Lanka		Rural	571	30–65	44.6	175	73	44.7	275	67	44.6	297
		Rural	331	30–65	45.9	48	50	45.4	139	47	46.3	192
		Rural	844	30-65	45.7	71	70	45.6	387	72	45.8	

FPG – fasting plasma glucose

*Estimated mean age based on age-group breakdowns.

†Sex-specific mean ages not provided, overall mean age used for both sexes.

Table 10. Individual study prevalence data: OGTT-only studies

AUTHORS	Country	Urban/	STUDY	Age range	Mean	O verall diabetes	Male diabetes	Mean	Size of	Female diabetes	Mean	Size of
		Rural	SAMPLE	OF PARTICI-	Age	prevalence (/1000	PREVALENCE	AGE	GROUP	PREVALENCE	AGE	GROUP
			SIZE	PANTS		POPULATION)	(/1000 men)			(/1000 women)		
Boddula et al (2008) [59]	India	Urban	1112	≥30	55*	246	284	55*	557	207	55*	555
Ramachandran et al (2004) [60]	India	Rural	1213	≥20	41	63	74	41.8	497	56	40.5	716
Ramachandran et al (1994) [61]	India	Urban	873	≥60	70*	237	_	_	_	_	_	_
		Rural	588	≥60	70*	99	_	_	_	_	_	_
Ramachandran et al (1992) [62]	India	Urban	900	≥20	38	82	103	40	457	61	37	443
		Rural	1038	≥20	41	24	27	41	520	21	41	518

OGTT - oral glucose tolerance test

*Estimated mean age based on hypothetical maximum age of 80.

Table 11. Overall	prevalence estimates	s for 2005
-------------------	----------------------	------------

Age range	Mean age (years)	Prevalence / 1000 population (y = 0.0368x ^{2.039})	2005 UNPD population estimates (× 1000)	Calculated 2005 prevalence estimates (× 1000)	PROPORTION OF BURDEN BY AGE GROUP (%)
20-24	22	20.09	152031	3055	4.64
25–29	27	30.51	134001	4088	6.21
30-34	32	43.14	115491	4982	7.57
35–39	37	58.00	102 984	5973	9.07
40-44	42	75.10	89614	6730	10.22
45-49	47	94.46	76802	7255	11.02
50-54	52	116.09	64131	7445	11.31
55-59	57	139.98	47010	6581	9.98
60-64	62	166.16	37 303	6198	9.41
65–69	67	194.63	29394	5721	8.69
70-74	72	225.40	20538	4629	7.03
75–79	77	258.47	12348	3191	4.85
		Total:	881647	65848	100.00
	2005 population				
				1 74	70/

prevalence:7.47%

UNPD- United Nations Population Division

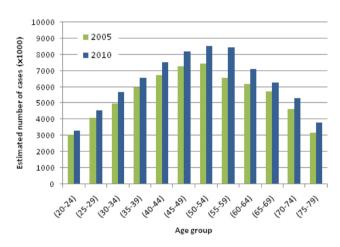


Figure 4. Estimated numbers of type 2 diabetes cases in Southern Asia (in thousands) by age group in 2005 and 2010.

2010 than for 2005: 7.60% compared to 7.47%. Figure 5 and Table 13 illustrate the relationship between diabetes prevalence and age for males (all diagnostic methods). Based on the trend line equations, male prevalence is slightly higher than female prevalence at all ages. At the extreme, estimated male prevalence for the 70–79 age group is 336.08 per 1000, whereas female prevalence is 297.57 per 1000. Figure 6 and Table 14 illustrate female age–specific prevalence for all diagnostic methods. Sex– and age–specific prevalence data are presented in **Supplementary Online Document**.

Table 12. Overall prevalence estimates for 2010

Mean age (years)	Prevalence / 1000 population (y = $0.0368x^{2.039}$)	2010 UNPD POPULATION ESTIMATES (×1000)	CALCULATED 2010 preva- lence estimates (\times 1000)	PROPORTION OF BURDEN BY AGE GROUP (%)
22	20.09	163363	3282	4.36
27	30.51	149024	4546	6.04
32	43.14	131390	5668	7.53
37	58.00	112937	6550	8.70
42	75.10	100 399	7540	10.01
47	94.46	86776	8197	10.89
52	116.09	73608	8545	11.35
57	139.98	60318	8444	11.21
62	166.16	42750	7103	9.43
67	194.63	32 320	6291	8.35
72	225.40	23627	5325	7.07
77	258.47	14742	3810	5.06
	Total:	991254	75302	100.00
	AGE (YEARS) 22 27 32 37 42 47 52 57 62 67 62	$\begin{array}{c} \text{AGE} & 1000 \text{ POPULATION} \\ (\text{YEARS}) & (\text{Y} = 0.0368 \text{x}^{2.033}) \\ \hline \\ \hline \\ 22 & 20.09 \\ \hline \\ 27 & 30.51 \\ 32 & 43.14 \\ 37 & 58.00 \\ 42 & 75.10 \\ 47 & 94.46 \\ 52 & 116.09 \\ 57 & 139.98 \\ 62 & 166.16 \\ 67 & 194.63 \\ 72 & 225.40 \\ 77 & 258.47 \\ \hline \end{array}$	AGE (YEARS) 1000 POPULATION (Y = 0.0368x ^{2.033}) UNPD POPULATION ESTIMATES (× 1000) 22 20.09 163363 27 30.51 149024 32 43.14 131390 37 58.00 112937 42 75.10 100399 47 94.46 86776 52 116.09 73608 57 139.98 60318 62 166.16 42750 67 194.63 32320 72 225.40 23627 77 258.47 14742	AGE (YEARS) 1000 population (Y = 0.0368x ^{2.039}) UNPD population ESTIMATES (× 1000) 2010 preva- lence estimates (× 1000) 22 20.09 163363 3282 27 30.51 149024 4546 32 43.14 131390 5668 37 58.00 112937 6550 42 75.10 100399 7540 47 94.46 86776 8197 52 116.09 73608 8545 57 139.98 60318 8444 62 166.16 42750 7103 67 194.63 32320 6291 72 225.40 23627 5325 77 258.47 14742 3810

2010 population prevalence: 7.60%

UNPD- United Nations Population Division

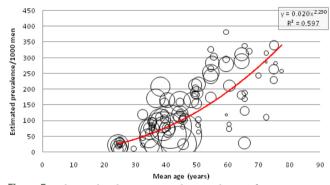


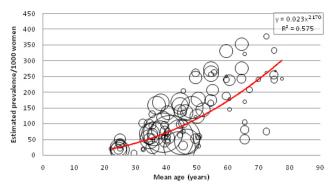
Figure 5. Relationship between crude prevalence of type 2 diabetes and age in Southern Asia in male examinees.

Ta	ble	13.	Male	preval	lence	estimates	for	2005
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Age range	Mean age (years)	Preva- lence/1000 men (y = 0.0208x ^{2.2308})	2005 UNPD male population	Calculated 2005 male prevalence	P ROPOR - TION OF BURDEN BY
			estimates ($ imes$ 1000)	estimates (× 1000)	AGE GROUP (%)
20-24	22	20.55	78574	1614	4.07
25–29	27	32.45	69157	2244	5.66
30–34	32	47.40	59699	2830	7.14
35–39	37	65.53	53 302	3493	8.81
40–44	42	86.94	46349	4029	10.17
45–49	47	111.73	39741	4440	11.21
50–54	52	140.00	32 984	4618	11.65
55–59	57	171.82	23669	4067	10.26
60–64	62	207.27	18546	3844	9.70
65–69	67	246.42	14386	3545	8.95
70–74	72	289.34	9985	2889	7.29
75–79	77	336.08	5979	2009	5.07
		Total:	452371	39622	100.00

2005 male prevalence: 8.76% 2005 corrected prevalence: 7.72%

UNPD- United Nations Population Division



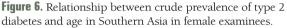


 Table 14. Female prevalence estimates for 2005

Age range	Mean age (years)	Prevalence/1000 women $(y = 0.0239x^{2.1708})$	2005 UNPD Female Population estimates (× 1000)	Calculated 2005 female prevalence estimates (1000)	PROPORTION OF BURDEN BY AGE GROUP
20-24	22	19.61	73457	1441	4.10%
25–29	27	30.59	64844	1984	5.65%
30-34	32	44.24	55792	2468	7.03%
35–39	37	60.62	49682	3012	8.58%
40-44	42	79.83	43265	3454	9.84%
45–49	47	101.90	37061	3777	10.76%
50-54	52	126.91	31147	3953	11.26%
55–59	57	154.90	23341	3616	10.30%
60-64	62	185.92	18757	3487	9.93%
65–69	67	220.01	15008	3302	9.41%
70-74	72	257.21	10553	2714	7.73%
75–79	77	297.57	6368	1895	5.40%
		Total:	429275	35102	100.00%
				ale prevalenc	
			_2005 corre	cted prevalen	ice: 7.20%

UNPD- United Nations Population Division

The crude population prevalence estimate for males in 2005 is 8.76% (39 622 000 cases), and for females is 8.18% (35 102 000 cases) (P < 0.001). These do not total the combined prevalence estimate of 65 848 000 cases (7.47%) since several studies did not provide enough data to calculate male and female age–specific prevalence, only enough to calculate combined sexes age–specific prevalence. To account for this incomplete data, the combined prevalence estimate was used as an envelope and a correction factor of 0.881 was applied to male and female prevalence estimates. Resultantly, the adjusted 2005 population prevalence estimates are 7.72% for males and 7.20% for females. Figure 7 illustrates a comparison between corrected male and female prevalence estimates at 5–year age intervals.

Urban and rural residency

32 out of the 39 selected studies (50 out of 57 cohorts) specifically defined their study population as residing in an urban area or a rural area. Incidentally, out of the reporting studies, 25 cohorts were specified as urban and 25 as rural. **Figure 8** illustrates diabetes prevalence against age in ur-

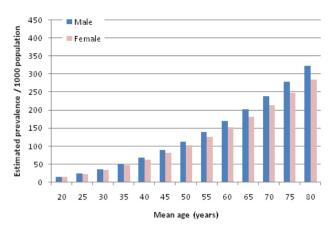


Figure 7. Male and female prevalence of type 2 diabetes in Southern Asia in 2005, adjusted to an "envelope" defined by all studies with prevalence data.

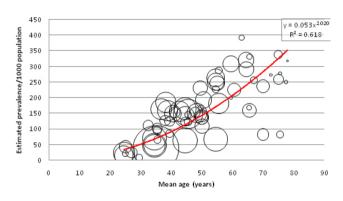


Figure 8. Crude prevalence of type 2 diabetes in Southern Asia in urban regions and its relationship with age.

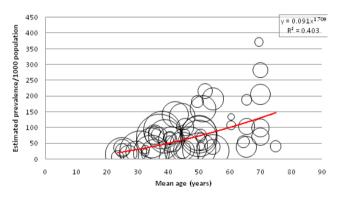


Figure 9. Crude prevalence of type 2 diabetes in Southern Asia in rural regions and its relationship with age.

ban cohorts (both sexes, all diagnostic methods), and Figure 9 does likewise for rural cohorts. Table 15 and Figure 10 highlight the prevalence differences observed between urban and rural cohorts. Figure 11 compares prevalence of diabetes in urban males with prevalence in rural males. Figure 12 compares prevalence of urban and rural females. In both cases urban residency is associated with signifi-

Table 15. Urban and rural overall prevalence comparison (*P*<0.001)

	-	-
Age (years)	Estimated urban prevalence/1000	ESTIMATED RURAL PREVALENCE/1000
	POPULATION (Y = $0.053x^{2.0206}$)	POPULATION (Y = $0.0917x^{1.7091}$)
20	22.55	15.34
25	35.40	22.47
30	51.16	30.68
35	69.86	39.93
40	91.50	50.17
45	116.08	61.36
50	143.62	73.46
55	174.12	86.46
60	207.59	100.32
65	244.03	115.03
70	283.45	130.56
75	325.86	146.90

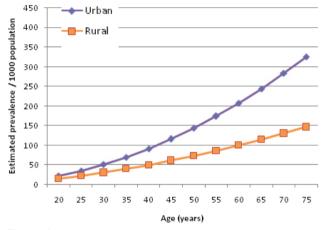


Figure 10. Comparison of the prevalence of type 2 diabetes in Southern Asia by age in urban and rural regions – both sexes included.

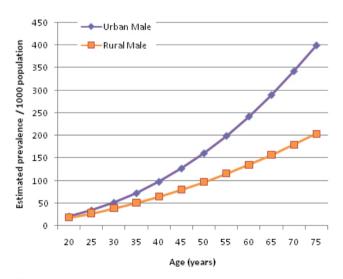


Figure 11. Comparison of the prevalence of type 2 diabetes in Southern Asia by age in urban and rural regions – men only.

cantly higher diabetes prevalence (P<0.001). Figures 13 and 14 show the estimates for both sexes by residency. Individual bubble graphs for residency are presented in **Online Supplementary Document**.

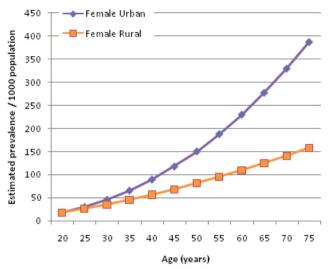


Figure 12. Comparison of the prevalence of type 2 diabetes in Southern Asia by age in urban and rural regions – women only.

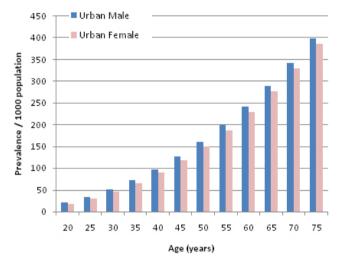


Figure 13. Male and female prevalence of type 2 diabetes in Southern Asia based on information from urban regions.

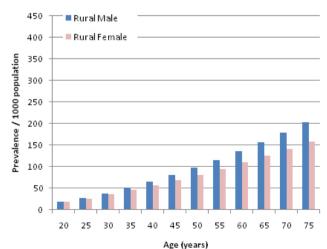


Figure 14. Male and female prevalence of type 2 diabetes in Southern Asia based on information from rural regions.

APERS

Method of diabetes diagnosis

Figure 15 shows the relationship between age and diabetes prevalence when only considering studies that utilised both FPG and OGTT in diagnosing diabetes. Figure 16 shows the relationship for studies that used only FPG, and Figure 17 shows OGTT-only studies. 65 age-specific data points were used to calculate the FPG+OGTT trend line, 77 data points used to calculate the FPG-only trend line, but due to the small number of available OGTT studies only 9 age-specific data points were used in calculating the OGTT trend line. Figure 18 compares the estimated prevalence using each of the three diagnostic methods. The combined FPG plus OGTT studies resulted in a higher population prevalence estimate than FPG-only studies when applied to UNPD figures, as shown by Table 16 and Table17. FPG plus OGTT studies result in a population prevalence of 7.75%, while FPG-only studies result in a prevalence of 7.32%. The small number of OGTT-only studies predicted a population prevalence of 6.95%, as shown in Table 18.

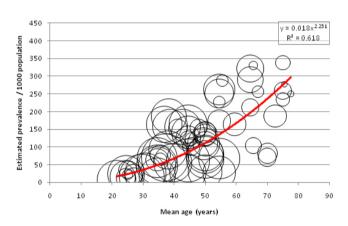
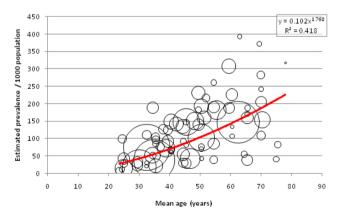


Figure 15. Relationship between crude prevalence of type 2 diabetes and age in Southern Asia based on the studies using FPG+OGTT in their case definition. FPG – fasting plasma glucose, OGTT – oral glucose tolerance test.



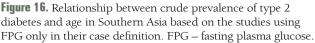


Table 16. Prevalence estimation	es for 2005 l	based on FPG+OGT	Г
studies			

Age range	Mean age (years)	$\begin{array}{l} Prevalence/1000\\ population\\ (y=0.0181x^{2.2319}) \end{array}$	2005 UNPD population estimates (× 1000)	Calcu- lated 2005 prevalence estimates (× 1000)	PROPORTION OF BURDEN BY AGE GROUP (%)
20-24	22	17.94	152031	2727	3.99
25–29	27	28.34	134001	3797	5.56
30-34	32	41.40	115491	4782	7.00
35–39	37	57.25	102984	5895	8.63
40-44	42	75.96	89614	6807	9.96
45-49	47	97.64	76802	7499	10.97
50-54	52	122.36	64131	7847	11.48
55–59	57	150.18	47010	7060	10.33
60–64	62	181.18	37303	6759	9.89
65–69	67	215.42	29394	6332	9.27
70-74	72	252.96	20538	5195	7.60
75–79	77	293.86	12348	3629	5.31
		Total:	881647	68330	100.00
				OGTT popul valence: 7.7 5	
			Overall p	opulation pr 005): 7.479	revalence

FPG – fasting plasma glucose, OGTT – oral glucose tolerance test, UNPD– United Nations Population Division

Table 17. Prevalence estimates for 2005 based on FPG-only studies

(years)	POPULATION ($y = 0.1021x^{1.7684}$)	population estimates (× 1000)	LATED 2005 PREVALENCE ESTIMATES (× 1000)	Proportion of Burden by Age Group
22	24.15	152031	3672	5.69%
27	34.69	134001	4649	7.20%
32	46.85	115491	5411	8.38%
37	60.57	102 984	6237	9.66%
42	75.78	89614	6791	10.52%
47	92.46	76802	7101	11.00%
52	110.56	64131	7090	10.98%
57	130.05	47010	6114	9.47%
62	150.90	37 303	5629	8.72%
67	173.08	29394	5088	7.88%
72	196.58	20538	4037	6.25%
77	221.36	12348	2733	4.23%
	Total:	88 647	64553	100.00%
		FPG–only population prevalence: 7.32%		
	22 27 32 37 42 47 52 57 62 67 72	22 24.15 27 34.69 32 46.85 37 60.57 42 75.78 47 92.46 52 110.56 57 130.05 62 150.90 67 173.08 72 196.58 77 221.36	(× 1000) 22 24.15 152.031 27 34.69 134.001 32 46.85 115.491 37 60.57 102.984 42 75.78 89.614 47 92.46 76.802 52 110.56 64.131 57 130.05 47.010 62 150.90 37.303 67 173.08 29.394 72 196.58 20.538 77 221.36 12.348 Total:	(× 1000) ESTIMATES (× 1000) 22 24.15 152 031 3672 27 34.69 134 001 4649 32 46.85 115 491 5411 37 60.57 102 984 6237 42 75.78 89 614 6791 47 92.46 76802 7101 52 110.56 64 131 7090 57 130.05 47 010 6114 62 150.90 37 303 5629 67 173.08 29 394 5088 72 196.58 20 538 4037 77 221.36 12 348 2733 Total: 88 647 64 553 FPG-only population FPG-only population

(2005): 7.47%

FPG - fasting plasma glucose, UNPD- United Nations Population Division

Table 18.	Prevalence	estimates	for 20	005 ł	based	on OG	TT–only
studies							-

Age range	Mean age (years)	$\frac{P_{REVALENCE}/1000}{POPULATION}$ $(y = 0.033x^{2.1118})$	2005 UNPD population esti- mates (× 1000)	Calcu- Lated 2005 Prevalence estimates (× 1000)	PROPOR- TION OF BURDEN BY AGE GROUP
20-24	22	8.52	152031	1295	2.11
25–29	27	15.74	134001	2109	3.44
30-34	32	26.21	115491	3026	4.94
35–39	37	40.51	102984	4172	6.81
40-44	42	59.25	89614	5309	8.66
45-49	47	83.03	76802	6377	10.41
50-54	52	112.44	64131	7211	11.77
55-59	57	148.09	47010	6962	11.36
60-64	62	190.58	37 303	7109	11.60
65–69	67	240.51	29394	7070	11.54
70–74	72	298.47	20538	6130	10.00
75–79	77	365.07	12348	4508	7.36
		Total:	881, 647	61278	100.00
			OGTT–only po	pulation pi 5.95%	revalence:
			Overall population prevalence (2005): 7.47%		

OGTT - oral glucose tolerance test, UNPD- United Nations Population Division

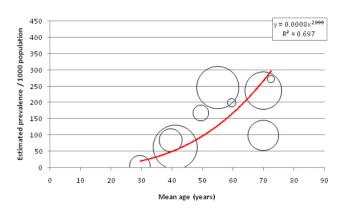


Figure 17. Relationship between crude prevalence of type 2 diabetes and age in Southern Asia based on the studies using OGTT only in their case definition. OGTT –oral glucose tolerance test.

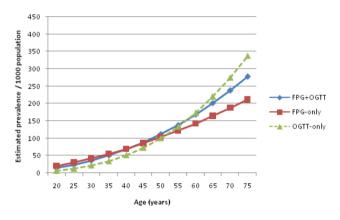


Figure 18. Comparison of the relationship between crude prevalence of type 2 diabetes and age in Southern Asia depending on the diagnostic methods used to establish case definition.

DISCUSSION

This study provides the most up-to-date transparent estimation of diabetes prevalence in the UN Southern Asia region, building upon previous studies looking at prevalence in comparable regions or in specific constituent countries [21,22,63,64]. It is also, to our knowledge, the first study to transparently estimate diabetes prevalence and trends in Southern Asia by synthesizing findings from numerous community-based studies in addition to broader national population studies.

A transparent systematic literature review of two online databases was carried out. Pre–defined inclusion and quality criteria narrowed down 39 studies from an initial 5653 results. Search terms were specified, and quality assessment criteria for selected studies were provided in Appendices. Enough studies were captured for estimation of overall diabetes prevalence, male and female prevalence, and urban and rural prevalence for each sex. Study cohort sites had a wide geographic distribution within the countries that were analysed, as shown in Figure 2. Additionally there was an even split of rural and urban studies, allowing for comparison of prevalence in both demographics. Data was not captured from all countries in the Southern Asia region the systematic literature review did not find any suitable studies from Afghanistan, Bhutan, or the Maldives. However, Table 5 shows that these three countries have the smallest adult populations in the region. For all other countries, including the three most populous countries of India, Pakistan, and Bangladesh, suitable numbers of geographically dispersed studies were identified. While this paper was able to adequately meet most of its set objectives, the small number of OGTT-only studies captured in the search meant that all recognised diagnostic methods could not be fully compared in terms of prevalence estimates, and so this objective was only partially met.

By applying this study's prevalence estimates to UNPD population Figures [23], the overall diabetes prevalence for the Southern Asia region was estimated to be 7.47% for 2005, and 7.60% for 2010. Although the reviewed studies were more representative of the year 2005, it is interesting to note the effects of an ageing population on diabetes prevalence. Estimates indicate that 25.0% of the regional population was aged 50 or older in 2010, compared to 23.9% in 2005. In addition, UNPD projections for Southern Asia predict that total population and life expectancy at birth for both males and females will continue to rise in the region over the next 30 years [23]. The findings of this study suggest that as the population continues to age in the future, the overall burden of diabetes in Southern Asia will also continue to increase, and that concerted policy action is needed to facilitate the response to this increased burden.

It was found that diabetes prevalence was consistently higher for males than for females. The burden was highest in the 50–54 age group for both sexes, and within this age group there was a 9.35% difference between estimated male and female prevalence. Prevalence/1000 population continued to increase with age for both sexes but due to the population age structure the burden attributed to older age groups was progressively smaller after the ages of 50–54. After correction for missing data, the 2005 population prevalence estimate for males was 7.72%, and for females was 7.20%. This translates into an estimated 34 915 000 male and 30 933 000 female diabetics in Southern Asia in 2005.

This study found that urban residency was strongly associated with higher diabetes prevalence for both sexes. The observed difference is noteworthy – past the age of 55 the urban prevalence was estimated to be more than twice the rural prevalence. Although males had higher prevalence than females in both urban and rural settings, the difference was noticeably smaller in urban cohorts than rural cohorts: a 6.03% difference between urban males and females, but a 16.74% difference between their rural counterparts. Higher rates of diabetes among urban residents may be explained through increases in physical inactivity and consumption of high sugar and fat diets – both strong risk factors for diabetes – that have become synonymous with urban lifestyles. Mohan suggested that diabetes rates in India are quickly escalating because of the rapid urbanisation that is sweeping the country [17]. Conversely, rural prevalence remains lower because of limited exposure to these risk factors and maintenance of traditional physically vigorous rural lifestyles.

Sufficient numbers of FPG-only and FPG+OGTT combined studies were identified to allow comparison between these two diagnostic methods. The small number of OGTT-only studies also provided interesting trends. Overall the differences between these methods appeared to be minimal. The higher prevalence estimates of FPG+OGTT compared to FPG-only were to be expected since the former used an additional diagnostic method. FPG-only studies estimated higher diabetes prevalence at younger ages (<52) and lower prevalence at older ages (>52) compared to OGTT-only. Combined FPG+OGTT prevalence estimates lay in between the FPG and OGTT estimates at both ends of the age spectrum. In addition, FPG-only studies estimated the highest burden proportion to be at a younger age - in the 45-49 age group - followed by a small decrease in the 50-54 age group. FPG+OGTT studies and the limited number of OGTT-only studies found highest burden proportion in the 50-54 age group. These findings suggest that FPG may have greater sensitivity at younger ages, while OGTT may be more sensitive to diabetes in older age.

This study's prevalence estimates were primarily based on trend line equations obtained by plotting study size, mean age and prevalence estimates on bubble graphs. Bubble graphs accommodate gaps in data better than weighted mean box–plots, and the resultant trend lines can be used to estimate the expected prevalence for any given age rather than just the specific age group means. Therefore, bubble graphs are preferable over weighted mean box–plots when considering a disease such as diabetes, for which the steady prevalence increase with age has previously been well established [21]. The trend lines obtained in this study all had high R² values – specified on each graph for purposes of transparency – indicating that they were representative of the data and took into account a high degree of variance.

Several of this study's findings are in line with previous estimations of diabetes burden in comparable regions. Estimates for 2000 [21] and 2010 [22] both suggest that in developing countries, diabetes burden is highest between the ages of 40 and 64, and lowest under the age of 40. This was reflected in the findings. Wild and colleagues also found that global diabetes prevalence was higher overall for males than females. However, more recent estimates for Southern Asia found no distinct increase in diabetes risk with male gender [64]. This study found a small but consistent difference between male and female prevalence. Based on national surveys for countries in the region, Jaywardena and colleagues estimated the overall Southern Asia diabetes prevalence to be in the range of 4.5–10.3% for the period 1995-2006[64]. This study's estimate of 7.47% for 2005 falls in the middle of this range. Additionally, this study's 2010 prevalence estimate of 7.60% is similar to the findings of Shaw and colleagues for the WHO region of South–East Asia[22], a geographic region that includes six out of the nine countries of the UN Southern Asia region (all apart from Afghanistan, Iran and Pakistan). Recent IDF estimations suggest that diabetes prevalence may be even higher - at an estimated 8.60% for South-East Asia in 2011 [65]. However, it is difficult to make comparisons between estimates for the UN Southern Asia region and the WHO South-East Asia region. In addition, different studies often use widely varying methods for study selection and estimating prevalence, contributing to the observed inconsistencies. Nevertheless, a substantial body of evidence including this study indicate that the diabetes burden in this area of the world is large and growing.

Limitations

This systematic review considered published studies from 1980–2013. However, suitable studies were only identified for the period 1992–2013. Not looking at studies prior to 1980 may have excluded viable studies, but older studies often used previous diabetes diagnostic criteria which underestimated prevalence. Most of the identified studies carried out prior to 1990 used the old 1980/1985 WHO criteria with the higher FPG cut–off of 7.8mmol/L for diabetes diagnosis. Including such studies in the analysis would distort the prevalence estimate because of the differing diabetes case definitions.

Several recent studies did not detail the diagnostic criteria used to identify diabetics, despite explaining their method of diagnosis. These studies were excluded to ensure that the case definition of diabetes in the selected studies remained constant. Other studies did not make it clear whether the biochemical samples they used were venous or capillary, or whether whole blood or plasma was analysed. WHO provides diagnostic guidelines for each of these sample types [11,12], but when sample type was not specified the study was excluded to minimise case definition misclassifications. Adherence to these stringent quality assessment criteria potentially limited the number of studies that could be included in this analysis. In addition, studies that did not diagnose diabetes through biochemical measurements but instead used techniques such as self-reported surveys were also excluded. Several studies had found low knowledge of diabetes in Southern Asia, even in diabetic patients [66,67], and therefore such methods were considered unreliable.

Studies investigating other forms of diabetes such as gestational diabetes or diabetes insipidus were excluded. These studies were easy to identify because of the specific nature of gestational diabetes, and the different clinical presentation of diabetes insipidus to diabetes mellitus (DM). However, a major limitation of this paper was the inadequate ability to distinguish between type 1 DM and type 2 DM. Many risk factors for type 2 DM, such as diet and physical inactivity, are modifiable and therefore may be amenable to policy intervention, but there are no known preventative measures against type 1 DM. Most analysed studies did not further investigate identified diabetics to exclude type 1 DM, meaning that this study's findings may be an overestimation of the prevalence of type 2 DM. However, in the adult age range that was being investigated, type 2 DM is more common than type 1 DM, hence their previous names of "adult-onset diabetes mellitus" and "childhood-onset diabetes mellitus". In addition, it has been noted that while type 1 DM rarely causes death by ketoacidosis in developed countries, sufferers in many developing countries may unfortunately have a radically shortened lifespan due to limited insulin availability which is crucial for type 1 DM management [68]. This may hold true especially for some of the poor rural areas investigated in this study. As a result, any error in the prevalence estimate due to type 1 diabetics is likely to be small.

Only published studies were reviewed. The resulting analysis may have suffered from publication bias as the reviewed papers may only show those studies in which significant results were found. Publication bias may have prevented studies that did not show significant diabetes prevalence from being published in the first place, preventing these studies from being captured in this review. While no limits were set on language, time constraints also prevented translation and therefore inclusion of non-English studies. This may have resulted in exclusion of viable non-English studies. However, even without setting language limits, only a very small number of non-English studies were identified by the literature search. This might be due to the status of English as an official language in several excolonial countries in the Southern Asia region, most notably India and Pakistan.

No suitable studies were identified for three out of nine of the countries in the region – Afghanistan, Bhutan, and the Maldives. As mentioned, however, these are the least populous countries in the region, and combined only account for 1.34% of the regional adult population. Nevertheless it is a noteworthy limitation that no data was available for these countries when the estimated regional population prevalence took their populations into account as well. Another limitation arose when comparing urban and rural studies. Cohorts were classified as urban or rural on the basis of individual study descriptions. No standardised definitions of 'urban' or 'rural' were used, meaning there may be discrepancies between different studies on their cohort classification.

Not all selected studies provided male and female sex-specific prevalence breakdowns, while others did not provide sample sizes for sex-specific prevalence or did not report mean age. This limited the number of cohorts that could be analysed for male and female age-specific prevalence. Where possible, sample sizes were calculated based on reported number of cases and corresponding prevalence figures. However, this study's findings were limited by assumptions that had to be made to account for incomplete data. UNPD national age structures were applied where appropriate [23]. This method of estimation may have increased imprecision as study populations are not necessarily representative of the national average. The use of a correction factor to account for incomplete sex-specific data may have been another source of imprecision. A hypothetical maximum age of 80 was used to calculate mean age for studies that provided no maximum age range. This assumption was made as this was the highest age used in reviewed studies that included a maximum age, and also because the minority of studies that looked at participants aged 80+ had very small sample sizes for those age groups. In addition, the 2005 UNPD population estimates for Southern Asia suggest that the 80+ age group accounts for only 0.58% of the population, so this was not considered a major limitation.

While every effort was made to ensure accuracy and the use of systematic methods, human error may have resulted in accidental exclusion of relevant studies when inclusion and quality criteria were being applied. Having only one person review and evaluate studies is a potential limitation of this study design. Using several independent evaluators to select studies, with a suitable method for resolving disputes, may increase reliability of the study's findings.

Implications for policy

Evidence on disease burden is essential for countries to plan and develop programs in response to the NCD pandemic. The WHO 2008–2013 Action Plan for the Prevention and Control of Noncommunicable Diseases highlighted that before prevention and control policies can be implemented, one of the first steps is to assess the burden of disease [69]. Engelgau and colleagues also proposed a framework for policy decision–making on NCDs[7], and improved surveillance is an essential component of their initial assessment stage. Several Southern Asian countries have shown improvements in their national NCD surveillance and monitoring capabilities in the last decade [2].

However, as previously discussed, estimates of diabetes burden vary widely between different sources. Further improvements in national surveillance capabilities are needed so that authoritative and standardised estimations of the burden of NCDs can be made. Accurate and up-to-date estimations of burden are also important in evaluation of current policies, programs, and of health system capacity. A number of policies have shown promise – in 2003 India enacted The Cigarette and Other Tobacco Products Act which is considered to have effectively reduced the public's exposure to tobacco smoke, through advertisement, and minors' access to cigarettes [7]. India also recently launched a pilot phase of the National Programme for Prevention and Control of Diabetes, Cardiovascular Diseases and Stroke (NPDCS), and has made financing commitments for the near future [70]. The aims of this program are laudable but monitoring of such programmes is necessary to ensure resources are used efficiently, and that appropriate targets and priorities are set [7]. This is of special importance due to rapidly-changing nature of NCDs and the many challenges that governments of developing Southern Asian countries face when attempting to deal with them.

The findings of this study suggest that future urbanisation and increased life expectancy will lead to a substantial rise in the burden of type 2 DM in the Southern Asia region. Commentators have noted that the process of population ageing currently being observed in developing countries is different to the demographic transition that occurred in developed countries several decades ago. In particular, the current demographic transition in developing countries has occurred on a faster scale than in developed countries, and without the associated improvements in living conditions, social provisions, and access to health care [7]. This has led to a 'compressed timeline' for developing countries to mount effective responses to growing NCD burdens compared to what developed countries had [1]. 'Unhealthy ageing' in Southern Asia due to these lagging improvements in nutrition and socioeconomic conditions is predicted to add to the natural increases in disease burden expected of an ageing population [7]. Therefore it is paramount that both prevention and treatment policy options are considered - the root causes of NCDs need to be addressed, and health system capacity should be reviewed to deal with the increasing burden.

Prevention efforts for diabetes can come in many forms, but there are several that may be especially relevant to Southern Asia. Before any successful prevention policies can be implemented it is important that knowledge and awareness regarding diabetes is improved in the general population. Many studies have shown that in Southern Asian populations, awareness of diabetes and its risk factors is poor [71,72], even among diabetic patients [66,67]. Population– level education and health promotion schemes should be put into place to improve awareness of the risk factors for diabetes and the other main NCDs. Diabetes has many lifestyle—modifiable risk factors, and by improving knowledge regarding these, the Southern Asian population can be empowered to pursue healthier lifestyle choices. Increased risk factor awareness and the resulting community empowerment have been seen to have a positive effect in the past. Mohan and colleagues reported that following such efforts, an Indian community was prompted to create a public park with their own funds which resulted in significant improvements in physical activity levels for local resident[73].

Departure from traditional dietary patterns and the uptake of diets high in saturated fats and heavily refined carbohydrates are believed to be important underlying factors in rising rates of obesity and diabetes in Southern Asia [17]. In particular, low intake of fibre, mono- and poly-unsaturated fats, and high consumption of refined carbohydrates, saturated fats and trans-fats have been identified as problematic dietary habits leading to insulin resistance in Southern Asian populations [74]. Policies should focus on addressing these unhealthy dietary patterns with a view to inform and educate. Successful policies from the health sector may include efforts to improve food labelling through dialogue with food companies, which when combined with education on NCD dietary risk factors may go some way to lowering diabetes and obesity incidence [7]. Focus should also be given on encouraging people to switch from traditional high trans-fat cooking oils such as ghee and vanaspati to poly–unsaturated alternatives [74].

The health sector has an important role to play in the management and treatment of NCDs. Table 2 shows that while all the Southern Asian economies are growing, many of them spend very small proportions of their gross domestic product (GDP) as health expenditure. In 2001, the WHO Commission on Macroeconomics and Health found that a basic set of essential health interventions costs approximately US\$34 per capita, believed to be a modest sum even for low-income countries [75]. However, several Southern Asian countries spend less on health than even this recommended minimum per capita expenditure [20]. NCDs undermine economic progress and have significant macroeconomic and microeconomic impacts [76]. The increasing burden of NCDs will strain existing health systems if health expenditure is not increased. Physician density is also low in many Southern Asian countries; Engelgau and colleagues suggest that improving region-wide health education and training capacities may help fill human resource gaps across the region by taking advantage of economies of scale [7].

Even if health system capacities are expanded to deal with the increasing burden of NCDs, access to appropriate health care remains a major challenge across the Southern Asia region. Studies in several Southern Asian countries have found significant personal expenditure and substantial financial loss associated with paying for diabetes treatment, with the main costs being the direct expenses of investigation, treatment, and hospital admission [49,77,78]. These expensive out–of–pocket medical costs are a major barrier for universal access to health care services in Southern Asia, and result in widening inequalities between rich and poor. In addition to increasing health care capacity, Southern Asian countries should aim to improve access to health care by implementing WHO universal coverage reforms [79]. Successful policy strategies may involve improving revenue collection by targeting tax avoidance; pooling risk to reduce cost–sharing; efficiency savings from introducing Health Technologies Assessment (HTA); and simply increasing the priority given to health and thereby increasing governmental health expenditure.

Implications for future research

Following the recent WHO addendum approving the use of HbA1_c as a diagnostic method [1], WHO and American Diabetes Association diagnostic guidelines and criteria are mostly aligned. Future studies investigating prevalence in a population or community should use these standardised methods and criteria for diagnosing diabetes to allow for informative comparison between studies. The utilisation of HbA1_c measurements also presents new avenues for diabetes epidemiological research. If appropriate quality assurance measures are put in place, as per WHO recommendations, HbA1_c presents a valuable method for investigating long term changes in glycaemic status in study subjects.

Studies calculating overall prevalence inadvertently calculate male and female prevalence as well, but as seen in this paper, in many cases these were not reported. Additionally many studies failed to report basic information such as mean age of sample, age group of sample, type of biochemical sample taken, or diagnostic criteria used to define diabetes. Access to this information would reduce the number of assumptions that have to be made for incomplete data, and additionally would allow for a more accurate estimate as far fewer studies would have to be excluded from analysis. As awareness of the need for large–scale population estimates of NCDs becomes more commonplace, it is hoped authors carrying out community–based studies begin to employ common standards to allow effective utilisation of their work in burden of disease analyses.

Diabetes is one end of a spectrum of glycaemic states, and future studies could estimate the burden of different forms of prediabetes as well. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are diagnosed with FPG and OGTT respectively so many studies report their prevalence alongside diabetes. Regional estimation of the burden of both prediabetes as well as diabetes would allow for a more comprehensive analysis of the challenges these hyperglycaemic diseases pose. This study found that diabetes is strongly associated with urban residency in Southern Asia. As the region continues a process of rapid globalisation and urbanisation, it is important to maintain diabetes surveillance in both urban and rural cohorts. Urban migration and the increasing accessibility of inactive, sedentary lifestyles suggest that the diabetes burden will increase in the future. Projections for 2030 predict that several Southern Asian nations will continue to rank among the countries with the largest numbers of diabetic residents [21,22]. However, monitoring and analysis of these vulnerable populations can inform public health policymakers and help manage the burden of diabetes. It is important that future studies focus on high–risk populations: urban residents, and, as life expectancy increases, the growing number of elderly people as well.

CONCLUSION

This systematic literature review found a high prevalence of type 2 DM in the Southern Asia region. Diabetes prevalence was associated with male gender, and strongly associated with older age and urban residency. On the basis of these findings this study also predicted that diabetes prevalence will continue to increase in the future as life expectancy in the region rises and countries continue to undergo processes of urbanisation. The findings of this study were consistent with several past studies, but dissimilar to the results of others. This highlights that inconsistent surveillance and conflicting estimations of burden are some of the many challenges faced by the Southern Asia region and its constituent countries in their effort to respond to the rising burden of NCDs.

Accurate and up-to-date estimates of burden of disease are essential for planning of policies, target and priority setting, as well as monitoring and assessment of existing programs. However, greater standardisation and shared principles are needed across different studies so that strong, clear messages are given to policymakers. It is hoped that improved surveillance capabilities in Southern Asian countries will encourage common standards for prevalence estimation to be established.

While current policies and programs on diabetes control have met with some success, the region faces numerous hurdles. Rising life expectancies coupled with 'unhealthy' ageing present a new set of challenges to those faced by developed countries several decades ago. Policies focusing on prevention have to deal with a population that largely has little awareness of diabetes and its risk factors, and is becoming increasingly accustomed to a sedentary lifestyle and unhealthy eating patterns. Health sectors also have their own set of issues – total health expenditure is low in many Southern Asian countries, there are significant human resource gaps, and already struggling health systems are predicted to be put under even greater strain as diabetes prevalence continues to increase. In addition, from an equity perspective, high cost—sharing coupled with the long—term care needed for NCDs such as diabetes means that access to health care may be limited for a large proportion of people in the region.

However, despite these numerous policy challenges and the projected increase in diabetes prevalence, slow progress is being made. NCDs are at the forefront of the international health agenda, several Southern Asian countries have greatly improved their NCD surveillance and monitoring capacities, and the numbers of studies estimating burden of type 2 diabetes mellitus appears to be increasing in recent years. Greater attention needs to be paid to this disease and its risk factors on national and regional levels in Southern Asia so that the growing burden of diabetes can be adequately addressed in the future.



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Competing interests: All authors have completed the Unified Competing Interest form at www.ic-mje.org/coi_disclosure.pdf (available on request from the corresponding author). The authors 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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Offline eLearning for undergraduates in health professions: A systematic review of the impact on knowledge, skills, attitudes and satisfaction

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A/Prof J Car 3 Fusionopolis Link, #03–08 Nexus@one–north Singapore 138543 josip.car@imperial.ac.uk **Background** The world is short of 7.2 million health–care workers and this figure is growing. The shortage of teachers is even greater, which limits traditional education modes. eLearning may help overcome this training need. Offline eLearning is useful in remote and resource–limited settings with poor internet access. To inform investments in offline eLearning, we need to establish its effectiveness in terms of gaining knowledge and skills, students' satisfaction and attitudes towards eLearning.

Methods We conducted a systematic review of offline eLearning for students enrolled in undergraduate, health–related university degrees. We included randomised controlled trials that compared offline eLearning to traditional learning or an alternative eLearning method. We searched the major bibliographic databases in August 2013 to identify articles that focused primarily on students' knowledge, skills, satisfaction and attitudes toward eLearning, and health economic information and adverse effects as secondary outcomes. We also searched reference lists of relevant studies. Two reviewers independently extracted data from the included studies. We synthesized the findings using a thematic summary approach.

Findings Forty–nine studies, including 4955 students enrolled in undergraduate medical, dentistry, nursing, psychology, or physical therapy studies, met the inclusion criteria. Eleven of the 33 studies testing knowledge gains found significantly higher gains in the eLearning intervention groups compared to traditional learning, whereas 21 did not detect significant differences or found mixed results. One study did not test for differences. Eight studies detected significantly higher skill gains in the eLearning intervention groups, whilst the other 5 testing skill gains did not detect differences between groups. No study found offline eLearning as inferior. Generally no differences in attitudes or preference of eLearning over traditional learning were observed. No clear trends were found in the comparison of different modes of eLearning. Most of the studies were small and subject to several biases.

Conclusions Our results suggest that offline eLearning is equivalent and possibly superior to traditional learning regarding knowledge, skills, attitudes and satisfaction. Although a robust conclusion cannot be drawn due to variable quality of the evidence, these results justify further investment into offline eLearning to address the global health care workforce shortage.

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The world is short of 7.2 million health–care workers and this figure is growing [1]. The shortage of teachers is even greater, which limits traditional education modes. Health workers are fundamental to ensuring equitable access to health services and achieving universal health coverage. In 2006, the World Health Organization (WHO) reported that fifty–seven countries were facing critical health workforce shortages due to lack of adequate training or migration (brain drain) [2]. Although major progress has been made to tackle the earlier estimated shortage of 4.3 million health workers globally [2], the numbers of health workers still need to be scaled up considerably [3] to achieve the Millennium Development Goals [4].

eLearning might help to address the training need for health workers. Many universities are already using eLearning to support traditional campus-based education or enable access to distance or flexible learning. Perceived advantages include reduction of the costs associated with delivery of educational outcomes [5], improving scalability of educational developments [6], increasing access and availability to education by breaking down geographical and temporal barriers and allowing access to experts and novel curricula [7].

eLearning is "an approach to teaching and learning, representing all or part of the educational model applied, that is based on the use of electronic media and devices as tools for improving access to training, communication and interaction and that facilitates the adoption of new ways of understanding and developing learning" [8]. It does not only differ from traditional learning (ie, face-to-face learning that takes place in a classroom environment) in the medium by which learning is delivered [9], but also affects the teaching and learning approaches used. eLearning can take the form of a full eLearning approach, which is entirely driven by technology, or be a mix of the traditional and fully computer-based methodologies (blended learning). Blended learning might be more suitable for health care training because of the need to combine hands-on skillsbased training at practical level as well as self-directed learning [10-14].

The United Nations (UN) and the WHO regard eLearning as a useful tool in addressing education needs in health care, especially in developing countries [15,16] where the worst health workforce shortages occur [2]. Currently, the most renowned eLearning initiatives focus on the online delivery of and online interaction with the learning materials. However, in resource–limited settings this approach is often not possible. Only 31% of the population had internet access in developing countries in 2013 [17]. Because network connectivity and bandwidth availability are key obstacles to effective delivery of eLearning content [9,18,19], a partially or completely offline eLearning approach may be more suitable in rural and/or developing areas. Offline computer–based eLearning delivered through eg, a CD–ROM or USB stick, for example, can be particularly efficient in increasing the accessibility, quality and availability of health related education within limited costs in remote areas with limited teaching staff, equipment, technological infrastructures and resources available. Assessing the effectiveness of these interventions for health professional education could provide an evidence base to guide and inform future projects and policies aimed at addressing the global shortage of health workers.

To our knowledge only 2 systematic reviews of randomised controlled trials (RCTs) assessing the effectiveness of offline eLearning have been conducted so far [20,21]. Both reviews were published over a decade ago. Besides, they only focused on dentistry [21] and medical [20] education.

We conducted a systematic review to compare the effectiveness of offline eLearning with traditional learning in terms of gaining knowledge and skills, students' satisfaction and attitudes towards eLearning.

METHODS

We conducted a systematic review following the Cochrane methodology [22].

Search methods for identification of studies

Electronic searches. We limited our electronic searches to records published on or after the year 2000 in order to highlight recent developments.

We developed a search strategy for MEDLINE (OvidSP) using a combination of keywords and MeSH terms that captured the types of intervention and the types of participants under evaluation in this systematic review (Table 1). We adapted the search strategy for use in EMBASE (OvidSP), PsycINFO (Ovid SP), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Educational Resources Information Center (ERIC) (ProQuest).

Where available, we used validated methodological filters to limit our searches to Randomised Controlled Trials (RCTs) and cluster RCTs (cRCTs). We ran the searches in August 2013.

Searching other resources. We checked reference lists of the included studies and systematic reviews of the literature identified by our electronic searches for additional studies.

Inclusion criteria

Types of studies and participants. We included studies published in any language on students of (i) undergradu-

Table 1. Search strategy for use in MEDLINE (Ovid SP)*

Ianic	" Search shalegy for use in MEDLINE (Ovid SP)
1.	exp Education, Distance/
2.	educat\$.mp.
3.	learn\$.mp.
4.	train\$.mp.
5.	instruct\$.mp.
6.	2 or 3 or 4 or 5
7.	"computer assisted".mp.
8.	Internet.mp
9.	distance.mp.
	web.mp.
11.	online.mp.
12.	virtual.mp.
13	
13.	"mobile phone".mp. "cell\$ phone".mp.
15.	smartphone
16.	smart-phone
17.	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18.	6 adj3 17
	exp Computer-Assisted Instruction/
20.	eLearning.mp.
21.	e-Learning.mp.
22.	mLearning.mp.
23.	m–Learning.mp.
24.	"virtual learning environment".mp.
25.	1 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26.	exp Education, Medical, Undergraduate/
27.	exp Education, Nursing/
28.	exp Medical Staff/
29.	exp Physicians/
30.	doctor?.mp.
31.	physician?.mp.
32.	exp Physician Assistants/
33.	exp Nurses/
34.	nurse?.mp/
35.	exp Nurses' Aides/
36.	exp Allied Health Personnel/
37.	exp Community Health Workers/
38.	exp Health Personnel/
39.	exp Health Manpower/
40.	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
	or 37 or 38 or 39
41.	25 and 40
42.	Randomized controlled trial.pt.
43.	Controlled clinical trial.pt.
44.	Randomized.ab.
45.	Placebo.ab.
46.	Drug therapy.fs.
47.	Randomly.ab.
48.	Trial.ab.
49.	Groups.ab.
<u> </u>	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51.	exp animals/ not humans.sh.
52.	50 not 51
53.	41 and 52
<u> </u>	Limit 53 to yr="2000 –Current"
	LIIIII JJ to yi = 2000 - Cullelli

*Source: Ovid MEDLINE® In_process& Other Non–Indexed Citations and Ovid MEDLINE® 1946 to Present. Date of search: 16 August2013 09:53. Limits: Year – 2000. Filter: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity–maximizing version (2008 revision); Ovid format.

ate, health–related university degrees; or (ii) basic, health– related vocational training programmes. We defined undergraduate education or basic vocational training as any type of study leading to a qualification that: (i) is recognised by the relevant governmental or professional bodies of the country where the studies were conducted; and (ii) entitles the qualification–holder to apply for entry level positions in the health care workforce. For this reason, graduate medical education courses from the USA were included.

We considered studies on candidates for and holders of the qualifications listed in the Health Field of Education and Training of the International Standard Classification of Education (ISCED–F) [23], except studies on students of traditional and complementary medicine. We hence included students reading dental studies, medicine, nursing and midwifery, medical diagnostic and treatment technology, therapy and rehabilitation, or pharmacy. Medicine and dentistry were classified under the umbrella term *allied health professions*.

Types of intervention. First, we conducted a systematic mapping of the types of technologies used by the included studies to deliver the learning materials, through which we identified 6 broad categories of eLearning interventions, based on the technologies employed: (1) Offline computer–based eLearning, (2) Online and local area network–based eLearning, (3) Psychomotor skills trainer, (4) Virtual reality environments, (5) Digital game–based learning and (6) mLearning.

We allocated each included study to the category that fitted the study best (definition of these categories is available in **Online Supplementary Document**).

We only included studies in which offline eLearning interventions were used to deliver the learning content, which we defined as *standalone applications where internet or intranet connections were not required for the delivery of the learning activities.* The eLearning software and interactions thus run entirely on a PC or laptop. Delivery channels of the software could be via CD–ROM or a USB memory stick. If the delivery mode of the software was based on a networked connection but the learning activities did not rely on this connection – ie, a replacement delivery channel could easily be identified with low efforts/costs, without any restrictions on original intended usage – then this is also an offline intervention.

Only studies that compared eLearning or blended learning methods to: (i) traditional learning; (ii) an alternative eLearning or blended learning method; or (iii) no intervention were eligible for inclusion. These studies could either be studies where eLearning was the sole means by which the intervention was delivered or where eLearning was part of a complex, multi–component intervention.

Types of outcome measures. To be eligible for inclusion, studies had to report at least 1 of the following primary or secondary outcomes:

Primary outcomes. Primary outcomes were: (1) Students' knowledge, measured using any validated or non–validated instrument (eg, pre– and post–test scores, grades, perceived knowledge survey scores); (2) Students' skills, measured using any validated or non–validated instrument (eg, pre– and post–test scores, time to perform a procedure, number of errors made whilst performing a procedure, perceived up–skilling); (3) Students' satisfaction and attitudes

towards eLearning, measured using any validated or non-validated instrument (eg, self–efficacy, satisfaction, accept-ability).

Secondary outcomes. Secondary outcomes were: (1) Health economic properties of the interventions (eg, implementation cost, return on investment); (2) Adverse and/or unintended effects of eLearning (eg, potential feelings of depression and loneliness, dropout risks [24] and "computer anxiety" [25]).

We only considered studies to have measured students' satisfaction and attitudes towards eLearning if they met all of the following criteria: (i) they compared the differences between intervention and control groups for these outcomes; (ii) the content of the survey questionnaires related to the teaching method (ie, eLearning method, blended learning, or traditional learning); and (iii) the adjectives used in the survey questionnaires accurately described attitudes and/ or satisfaction.

Study selection and data collection

The study selection process is summarised in the PRISMA flow diagram (Figure 1). In brief, we screened the titles and abstracts of the citations identified by our electronic

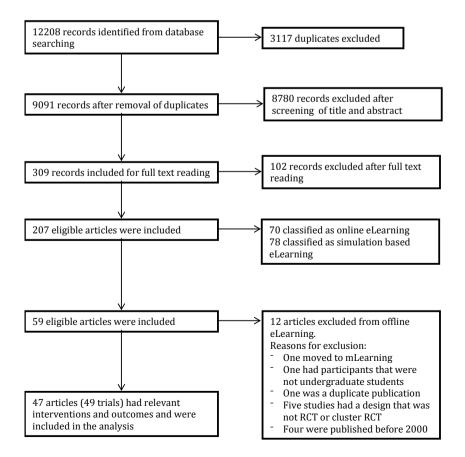


Figure 1. Flowchart of the studies included in the review.

and manual searches to identify potentially relevant studies, of which we assessed the full-text report to ensure they meet the inclusion criteria we specified. Review authors completed these tasks independently and met to compare their results and reach consensus.

Every selected study was allocated to a pair of review authors, with ten review authors participating in total. Each review author independently extracted data from the included studies using the structured data extraction sheet shown in **Online Supplementary Document**.

Each pair of reviewers compared their completed data extraction forms and any discrepancies between review authors' results were resolved through discussion; if no agreement could be reached, a third review author acted as an arbiter. Because ten review authors participated in the data extraction process, some categories were interpreted differently by some reviewers. Therefore, 3 reviewers went over the entire data extraction again to ensure uniformity.

We contacted authors of studies containing incomplete data to request the missing information. Some authors did not reply to our request for additional information, whilst other authors did not know the answer to our questions. For a single study, the response obtained from the author

resulted in the subsequent exclusion of the study from the systematic review.

Assessment of risk of bias in included studies

During the data extraction process, we assessed the risk of bias at the outcome level using tools recommended by the Cochrane Collaboration [22]. For RCTs, we did so across the domains of (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other bias including the comparability of intervention and control group; characteristics at baseline; validation of outcome assessment tools; reliability of outcome measures; and protection against contamination.

We assessed the risk of bias for cRCTs across the domains of (1) recruitment bias, (2) baseline imbalances, (3) loss of clusters and (4) incorrect analysis.

For each study, 2 reviewers independently categorised each domain as low, high or unclear risk of bias.

Summarising the data

We qualitatively compared the characteristics of the participants and of the interventions between the included studies to determine the feasibility of conducting a meta– analysis. Because of substantial clinical, educational, content and methodological heterogeneity we did not conduct a meta–analysis. Instead, we adopted a thematic summary approach [26].

RESULTS

The study selection process is depicted in Figure 1. The initial search yielded 12 208 records. After removing 3117

duplicate records using EndNote X5, we screened the titles and abstracts of 9091 records (see **Online Supplementary Document** for a detailed description). After this initial screening, we excluded 8780 records. We retrieved the full text reports for the remaining 309 records and assessed them for eligibility. Of these, we excluded 102 articles that did not meet the eligibility criteria (Figure 1).

Forty–seven [27–73] of the remaining articles complied with the term *offline eLearning*.

Two [54,70] articles reported results of 2 separate cRCTs that were analysed separately, and 2 articles [43,74] reported results from the same study. This resulted in a total number of evaluated studies of 49 (Table 2).

Table 2	2. Summary	v of findings fo	or the 40 studies	comparing of	offline eLearnin	g with traditional	learning
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Study	DISCIPLINE	Knowledge	Skills	ATTITUDE	Satisfaction	No. of participant	INTERVENTION DELIVERY APPROACH	Characteristics
Ackermann 2010 [27]	Medicine	E				19	Full eLearning	CG: Lecture IG: CD–ROM
Amesse 2008 [28]	Medicine	E				36	Full eLearning	CG: Paper based tutorial IG: Computer based tutorial
Armstrong 2009 [29]	Medicine					21	Full eLearning	CG: Lecture IG: Interactive slideshow
Bains 2011 [30]	Dentistry	NS		E		90	IG 1: Full eLearning IG 2: Blended learning IG 3: Blended learning	CG: Teacher–led tutorial IG 1: Online tutorial only IG2: Online tutorial only, then teacher–led tutorial IG3: Teacher–led tutorial, then online tutorial only
Bloomfield 2010 [31]	Nursing	NS	М			223	Full eLearning	CG: Lecture/video/practice IG: Computer module including video
Boet 2010 [32]	Medicine		М			42	Blended learning	CG: Lecture IG: Lecture + CD–ROM
Bogacki 2004 [33]	Dentistry	NS				45	Full eLearning	CG: Lecture IG: Computer program
Bradley 2005 [34]	Medicine	NS		NS		168	Full eLearning	CG: Workshops IG: Workbook + CD–ROM
Davis 2008 [35]	Nursing	NS				179	Blended learning	CG: Lecture IG: Digital recording + PowerPoint slides + Internet links
Feeg 2005 [36]	Nursing	E				91	Blended learning	CG: Journal article
Gelb 2001 [37]	Medicine	NS				107	Full eLearning	IG: Journal article + CD CG: Printed tutorial IG: Computer tutorial
Glicksman 2009 [38]	Medicine		Е	Е		47	Full eLearning	CG: Article IG: Computer module with article
Goldsworthy 2006 [39]	Nursing	Е				25	Full eLearning	CG: Paper–resources IG: PDA–based resources
Green 2011 [40]	Medicine	E			E	121	Full eLearning	CG: Paper–based resources IG: Computer program
Holt 2001 [41]	Medicine	NS				108	Full eLearning	CG: Lectures IG: Computer–based lectures
Howerton 2002 [42]	Dentistry	NS				59	Blended learning	CG: Lectures IG: CD–ROM
Jeffries 2003 [45]	Nursing	NS	NS	NS	NS	73	Full eLearning	CG: Self–study module + instructor led demonstration IG: Self–study module + CD
Kim 2003 [48]	Nursing	NS	NS	NS	E	75	Blended learning	CG: Printed material IG: Computer–based material
Kong 2009 [49]	Medicine	E	E		Ε	90	IG 1: Blended learning IG 2: Other learning	CG: Didactic teaching IG 1: Paper–based Problem Based Learning IG 2: Computer–based Problem Based Learning

Study	DISCIPLINE	Knowledge	Skills	ATTITUDE	SATISFACTION	No. of participants	Intervention delivery approach	Characteristics
Kurihara 2004 [50]	Medicine	E	E			59	IG 1: Full eLearning IG 2: Blended learning IG 3: Traditional learning	CG: Textbook only IG 1: Computer program only IG 2: Textbook + Computer program
Lira 2013 [51]	Medicine	М				68	Blended learning	IG 3: No intervention CG: Lecture IG: Lecture + PDF article
Maleck 2001* [52]	Medicine	DNT		М	Τ	192	IG 1: Full eLearning IG 2: Full eLearning	G: Lecture + PDF atticle CG: Paper cases, textbook + optional lecture IG 1: Computer–based cases, textbook + optional lecture IG 2: No cases, optional text- book + lecture
McDonough 2002 [53]	Medicine	NS			Т	37	Blended learning	CG: Lecture + tutorial IG: Lecture + computer tutorial
McMullan 2011a† [54]	Nursing	E		NS	E	48	Full eLearning	CG: Paper hand–out IG: Computer program
McMullan 2011b [54]	Nursing	E		E		50	Full eLearning	CG: Paper hand–out IG: Computer program
Miedzybrodzka 2001 [55]	Medicine	NS		NS		48	Full eLearning	CG: Lecture IG: Computer program
Nance 2009 [57]	Dentistry		NS	E		73	Full eLearning	CG: Paper hand–out+laboratory session IG: DVD only
Nola 2005 [58]	Medicine	E				85	Full eLearning	CG: Lectures + practical sessions IG: Lectures (optional) + computer- ised sessions
Perfeito 2008 [60]	Medicine	NS				35	Full eLearning	CG: Lecture IG: Computer program
Qayumi 2004 [63]	Medicine	E	E			99	IG 1: Traditional learning IG 2: Full eLearning IG 3: Blended learning	
Roppolo 2011 [64]	Medicine		E			180	IG 1: Blended learning IG 2: Blended learning	CG: Instructor and video based course (cognitive) + Instructor led course (practical) IG 1: Online course (cognitive) + DVD-based course (practical) IG 2: Online course (cognitive) + Facilitator based practice (practical)
Seabra 2004 [65]	Medicine	NS				60	Full eLearning	CG: Lecture IG: Computer program
Shomaker 2002† [66]	Medicine	NS			DNT	94	IG 1: Full eLearning IG 2: Blended learning	CG: Lectures, texts + slides IG 1: Computer program + texts IG 2: All of the above
Solomon 2004 [67]	Medicine	NS				29	Full eLearning	CG: Lecture IG: CD–ROM
Vichitvejpaisal 2001 [69]	Medicine	М				80	Full eLearning	CG: Textbook IG: Computer program
Vivekananda–Schmidt 2005a [70]	Medicine		E	NS		105	Full eLearning	CG: No CD–ROM IG: CD–ROM
Vivekananda–Schmidt 2005b [70]	Medicine		Е	Е		156	Full eLearning	CG: No CD–ROM IG: CD–ROM
Weih 2008 [71]	Medicine and Psycholog				Е	101	Full eLearning	CG: Lecture IG: Lecture + CD–ROM
Williams 2001 [72]	Medicine					163	Full eLearning	CG: Lecture IG: Computer program
Xeroulis 2007 [73]	Medicine		E			60		CG: No intervention IG 1: Computer–based video IG 2: Concurrent feedback during practice IG 3: Summary feedback after practice

E – Results favoured computer–based eLearning over traditional learning, NS – No significant difference between eLearning and traditional learning, M – Mixed results, T – Results favoured traditional learning over computer–based eLearning, DNT – Difference not tested, CG – Control group, IG – Intervention group

*Knowledge improvement in the two eLearning groups as well as the traditional learning group, whereas the control group that received no intervention, showed minimal improvement.

†In the cRCT by McMullan 2011 [55], the results for satisfaction were pooled for the two cohorts (McMullan 2011a and McMullan 2011b) and the result presented for McMullan 2011a therefore also includes students from the McMullan 2011b cohort.

‡For students' satisfaction, no clear trends in terms of one intervention group being superior to another.

Included studies

The 49 included studies were either parallel RCTs or cRCTs published in peer–reviewed journals between 2001 and 2013. There were no clear trends in terms of increase in publication of offline studies in the time period investigated. Thirty–five studies [27–29,32,34,37,38,40,41,44, 46,47,49–53,55,5,58–70,72,73] investigated eLearning in the field of medicine, 8 in the field of nursing [31,35,36, 39,45,48,54] and 4 in the field of dentistry [30,33,42,57]. One article [71] focused on both medicine and psychology whereas another [43] focused on medicine, dentistry and physical therapy at the same time.

Participant characteristics

The total number of participants included across all trials was 4955. The smallest study included 8 participants in the control and 8 participants in the intervention group [59]. The study with the largest control group had 177 participants [58], while the largest intervention group had 113 participants [31]. Most studies were conducted among undergraduate university students apart from 2 studies [31,36] that investigated the effect of offline eLearning for vocational training. Eleven studies that specified the age of the students. In the control groups, the mean age of participants ranged from 22.4 [30] to 30 years [35]. The mean age of participants in the control group was comparable, ranging from 21.8 [30] to 30 years [35].

Intervention characteristics

Forty studies [27–42,45,48–55,57,58,60,63–67,69–73] compared eLearning to traditional learning and 9 studies [43,44,46,47,56,59,61,62,68] compared one mode to another mode of eLearning. The shortest duration of exposure was 20 minutes [47] and the longest was 1 year [58].

Most of the studies (42 out of 49; 86%) were conducted in high–income countries, and 13 of these [28,33,36,37,40,42,45,47,57,64,66–68] in the USA. The remaining 5 studies were conducted in low– and middle–income countries: 1 [69] in Thailand; 1 [49] in China; and 1 [51,60,65] in Brazil. Figure 2 shows the distribution of the countries in which the studies were conducted.

The majority of the studies used programs that run on PCs or laptops [27–38,40–73]. One study [39] investigated the use of a Personal Digital Assistant (PDA), which is a small portable electronic device that can be regarded as the predecessor of a computer tablet and smartphone, with PDFs from Elsevier. Sixteen studies delivered the eLearning intervention to the students on a CD–ROM. [27,28,32–36,42,45,48,49,60, 67,70,71]. The eLearning software and material used in the remaining studies were distributed via a variety of sources where specified: learning management systems such as WebCT Blackboard [30,43], DVDs [30,57,61], the internet [29,47,51], stored on a computer [53,58,69] or for 1 study [39] on a PDA, and email [56], Several interventions used standard vendor software such as Adobe® [51,54], Macromedia AuthorWare® [66] and Microsoft® PowerPoint® [29,36].

Primary outcomes

Students' knowledge assessment. Overall, 40 [27–31,33–37,39–45,47–56,58,60–63,65–69,71,72] out of the 49 studies looked at a knowledge based outcome. Nineteen of these [29–31,34,36,37,40,41,43,45,47,50,51,53,61,63, 65,71,72] used only a multiple choice questionnaire (MCQ) to test students' knowledge and understanding, while another 9 studies [27,35,44,52,55,56,58,60,66] used a MCQ in conjunction with an additional testing method (eg, short answer questions or X–ray image interpretation). A further eleven studies [28,39,42,48,49,54,62, 67–69] measured students' knowledge gain via other testing means including case analysis, X–ray image interpretation and written exams. One study [33] did not specify which method was used to examine the participants' knowledge.

Students' skills assessment. Skills were assessed in 16 studies [31,32,38,45–50,57,59,63,64,70,73], the method of which was described in all but 1 study [49]. Ten of these [31,38,45,47,48,50,63,64,70] used a rating scale and/or checklists (eg, an Objective Structured Clinical Examination – OSCE) to assess clinical skills. Three studies [46,59,73] used the Imperial College Surgical Assessment

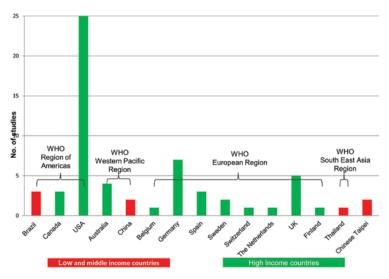


Figure 2. Country of origin of included, examined studies for low– and middle–income and high income countries separately

Device and a checklist for the assessment. Another study [57] used a grading rubric to assess ability to carve teeth in wax. Another study assessing the ability to conduct orotracheal fibreoptic intubation [32] evaluated successful intubation in real time.

Students' satisfaction and attitudes towards eLearning assessment. None of the studies assessed change in students' professional attitudes towards patients such as compassion.

Feedback from students assessed as their attitude towards the eLearning intervention was reported as an outcome in 14 studies [30,34,38,45,48,52,54–57,61,70]. Participants were asked to provide ratings via Likert scales in 11 studies [34,48,52,54–57,61,70]. One study [38] used a questionnaire and did not mention the use of Likert scales. In the remaining 2 studies [30,45], Likert scales were combined with another method, ie, focus groups in Bains et al. [30] and an additional questionnaire in Jeffries et al [45].

Students' satisfaction was considered as an outcome in 13 studies [40,43,45,48,49,52–54,61,62,66,71]. Eight of these studies [40,43,49,53,54,61,62] specified that students' satisfaction was evaluated with Likert scale questionnaires. The 5 remaining studies comparing students' satisfaction among the students [45,48,52,66,71] used different types of questionnaires without mentioning the use of Likert scales.

Secondary outcomes

Health economic properties of the eLearning intervention. Health economic properties of the eLearning intervention were rarely mentioned in the included offline eLearning studies. However, some of the studies addressed certain financial and resource related elements of eLearning. Davis et al. [35] mentioned that costs in producing the eLearning package were minimal and well within normal departmental budgets for teaching undergraduates. Ackermann et al. [27] stated that effective learning can be performed with the use of few resources and provides a very economical mode for educating medical students. Bradley et al. [34] stated that the in-house development of the eLearning course material took 40 hours for the preparation of the course material, 10 hours to administer each semester and the internet site used for the eLearning group took 100 hours to develop. The eLearning course material also included a CD-ROM produced externally with an estimated cost of £ 30 per CD [34]. McDonough et al. [53] reported that it took local IT staff 4 hours to install the program on 20 PCs and that no maintenance was required after that point. Vivekananda-Schmidt et al. [70] stated that the costs of designing the eLearning course were £ 11740 (US\$ 22045). Tunuguntla et al. [68] wrote in reference to comparing 2 different types of eLearning: "The cost ratio (measured in hours) for the module was about 2:3: about 72h for creation of the static graphics vs. 106h for the animations".

Adverse or unintended effects of eLearning. Adverse or unintended events of the eLearning intervention were not reported in any of the studies.

Excluded studies

Initially 59 articles were categorised as offline eLearning studies. One study [75] was reclassified as mLearning because lectures were viewed on an iPod [75], and was therefore excluded from this systematic review. Eleven studies [74,76–84] were excluded during the data extraction phase because they met 1 or more of the exclusion criteria. Four studies [77,78,83,85] of these were published before 2000. Five studies [79–82,84] were excluded because the study design was not a parallel or cRCT. One study was excluded as the participants were not undergraduate students [76]. An additional study [74] was a secondary publication of a study that was already included [43] and information from the secondary publication was merged with the included study.

Risk of bias in included studies

The assessment of risk of bias is described in detail in **Online Supplementary Document**. In summary, the majority of the included parallel RCTs were considered to be of low quality because of high risk of bias [28,31–34,36,38– 44,47,50–52,56,57,62,63,66–69,71]. Only a few studies [27,37,46,48,49,53,55,58–61,65,66,72,73] were of high quality with none of the assessed categories rated as having a high risk of bias (**Figure 3 and 4**). In the majority of studies at least 1 or more categories were classified as having an unclear risk of bias, especially with regards to the allocation of participants to intervention groups.

Effects of offline eLearning interventions

The 49 randomized trials included in our review assessed the effectiveness of offline eLearning interventions in terms of knowledge, skills, attitudes and satisfaction. The findings were based on comparisons between offline eLearning and traditional learning or between various modes of offline eLearning. A study may have compared more than 1 outcome between groups, and each outcome may have been assessed in multiple ways. For example, a study which compared students' acquisition of skills may have assessed skills in terms of the student's performance on a global rating scale, ability to perform a specific procedure as well as the ability to comply with requirements in a checklist. As a result, the number of comparisons made across studies for a particular outcome may exceed the number of studies which reported that outcome.

The studies were split into 2 research themes evaluating the impact of eLearning interventions for undergraduate APERS

health care education: traditional learning vs offline eLearning, and offline eLearning vs offline eLearning.

Traditional learning vs offline eLearning

Forty (82%) of the included studies [27–42,45,48–55,57, 58,60,63–67,69–73] compared offline eLearning with traditional learning. Please refer to Table 2 for a summary of findings of the individual studies, and to **Online Supplementary Document** for a further description of the nature of the interventions.

Students' knowledge. Amongst the 40 studies which compared offline eLearning with traditional learning, knowledge was assessed in 33 (83%) studies [27-31,33-37,39-42,45,48-55,58,60,63,65-67,69,72], 5 of which were cRCTs [29,30,45,54]. Eleven (33%) studies [27,28,36,39,40,49,50,54,63] assessing knowledge gain demonstrated significantly higher knowledge gains for students assigned to offline eLearning compared to those exposed to traditional learning. Outcome measures for these studies were based on correct responses to questions which included true-false, multiple choice or fill in the blanks type of assessments. The sample size for these studies ranged from 19 to 225 with all but 4 studies [36,39,54] conducted on medical students. Seven of these studies used solely offline eLearning as the main intervention [27,28, 39,40,54,63,84] whereas 4 used blended learning [36,42, 49,58].

None of the included studies found greater gain in knowledge for the traditional learning group.

Post–intervention knowledge was not significantly different between eLearning and traditional learning in 19(58%) of the included studies [29–31,33–35,37,41,42,45,48,53, 55,60,65–67,71,72].

Two (6%) studies [51,69] showed mixed results ie, favouring the intervention, control, or neither 1 depending on the specific indicator of knowledge being assessed. Another study [51] initially found no difference between the traditional and offline eLearning groups, but statistically sig-

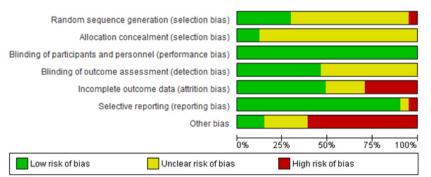


Figure 3. Overall risk of bias graph.



nificantly better post-test scores were seen in the offline eLearning group after 1 month. Another study [69] showed that students taught blood gas interpretation using a textbook had greater improvement from pre-test to post-test compared to those in the offline eLearning group, but after 3 weeks the final test scores of both groups failed to show a significant difference between the 2 groups.

In 1 (3%) study [52] knowledge was assessed, but not tested for statistically significant differences between the intervention groups. The study showed knowledge improvement in the 2 offline eLearning groups as well as the traditional learning group, whereas the control group that received no intervention showed minimal improvement.

Students' skills. Overall, 13 studies – 9 RCTs [31,32,38,48–50,57,63,73] and 4 cRCTs [45,64,70] measured skills as an outcome.

Of the studies that evaluated differences in skills acquisition, 8 (62%) [38,49,50,63,64,70,73] found significantly greater skills acquisition amongst students assigned to offline eLearning compared to those assigned to traditional learning. The range of skills assessed by these studies included performance in specific tasks, such as cardiopulmonary resuscitation, fiberoptic intubation and knot tying skills; performance in objective structured clinical examination, as well self–efficacy assessments. The number of participants included in these studies ranged from 19 to 354. All 8 studies [38,49,50,63,64,70,73] were conducted in medical students. Three (23%) studies [45,48,57] did not detect a significant difference in skill acquisition between groups.

None of the 13 studies demonstrated more favourable results for traditional learning compared to offline eLearning.

Results were mixed for 2 (15%) studies [31,32]. In 1 of these [31], testing hand washing skills of nursing students assigned to computer assisted vs conventional learning, skills were similar in both groups at the 2–week follow–up but were in favour of the intervention group at the eight– week follow–up. In the other study [32] that focused on intubation skills, successful intubation was more common in the offline eLearning group compared to the traditional group whereas there was no statistical significant difference in the checklist and global rating scale assessment of intubation skills.

Students' satisfaction and attitudes towards eLearning. Twelve studies – 6 RCTs [34,38,48,52,55,57] and 6 cRCTs [30,45,54,70] – assessed attitudes towards the eLearning the intervention, primarily through Likert scale surveys.

Five (42%) studies [30,38,54,57,70] found more favourable results for students assigned to eLearning compared to traditional learning. Six (50%) studies [34,45,48,54,55,70] did not detect a statistically significant difference in attitudes toward eLearning between groups. None of the studies found more favourable attitudes towards traditional learning.

One study [52] that assessed the difference between traditional learning and 2 different types of eLearning (8%) showed mixed results. The comparison between the traditional learning group and the eLearning group with no interaction (ie, offline eLearning cases with no tests) showed that statistically significantly more students would recommend eLearning group with no interaction. However, the comparison between the control and the eLearning group with interaction (ie, cases with multiple choice and free– text questions) did not show a statistically significant difference [52].

Students' satisfaction was assessed in 7 RCT studies [40, 48,49,52,53,66,71] and 2 cRCT studies [45,54].

Out of 9 studies looking at the level of students' satisfaction, 5 (56%) studies [40,48,49,54,71] found a significantly greater proportion of students who were satisfied among those exposed to eLearning as compared to those exposed to traditional learning. Students' satisfaction was based on questionnaires, surveys and global perceptions of satisfaction.

Two of the studies [52,53] showed higher satisfaction levels for students assigned to traditional learning groups.

One (11%) study [45] did not detect any significant difference while another study (11%) [66] did not test for significant differences and there were no clear trends in terms of 1 intervention group being superior to another.

Comparison of different types of offline eLearning against each other

Nine (18%) [43,44,46,47,56,59,61,62,68] of the included studies compared the effectiveness of various modes of offline eLearning against each other.

Students' knowledge. Seven (78%) studies [43,44,47, 56,61,62,68] compared various forms of offline eLearning and their effects on knowledge. A study [43] comparing the effectiveness of 3D vs 2D images of the larynx projected on a computer screen demonstrated higher test scores for students assigned to view 2D images. Another study [61] assessing the effectiveness of an actual video of ophthalmic procedures vs actual video supplemented with 3D video demonstrated higher scores on theoretical knowledge for the group assigned to 3D video.

One study [56] comparing 2 types of eLearning for teaching a module on leukaemia found that the more interactive eLearning intervention including questions resulted in statistically significantly higher mean percentage scores on the post-test on leukaemia compared to the more passive intervention group who only saw text and had no questions to answer.

No differences were found in 3 studies [44,47,68] comparing different eLearning modalities with each other. Two of the studies [44,47] compared groups of eLearning with different levels of student interaction with each other, whereas 1 group received no intervention. The third study [68] compared the effects of 2 versions of a program, 1 with animations and 1 with static graphics.

One study [62] showed mixed findings, with 1 offline eLearning mode exhibiting superior results with respect to a particular knowledge test and another offline eLearning mode exhibiting better results with respect to a different knowledge test.

Students' skills. Skill acquisition was assessed in 3 (33%) [46,47,59] of the 9 studies which compared different offline eLearning modalities. Out of the 3 studies which assessed skill, 1 study [47] demonstrated better skill acquisition with the use of a particular mode of offline eLearning over other modes. That study investigated the effects of 3 different methods of manipulating contents for learning abdominal examination: click, watch and drag. Their results showed that students who were able to use the mouse to trigger animated demonstrations ('click') performed better in auscultation than those who were in a more passive learning group where students only had control over the pace of the presentation ('watch'). The same group ('click') outperformed students who were in a more active learning group where students were able to drag tools in motions simulating actual performance of the task ('drag') in terms of abdominal palpation and additional manoeuvres. In addition, more students in the 'drag' and 'click' groups correctly diagnosed a simulated patient as having appendicitis than students in the 'watch' group.

Two studies [46,59] failed to demonstrate any difference in skill acquisition between eLearning modes.

Students' satisfaction and attitudes towards eLearning. Prinz et al. [61] and Morgulis et al. [56] were the only studies amongst the 9 studies comparing different eLearning modalities that assessed attitudes towards eLearning. The study by Prinz et al. showed that the students in the 3D group rated the learning aid in the 3D group more useful compared to the control group students' rating of the learning aid available in the control group and the difference was statistically significant. Intelligibility for glaucoma surgery and improvement of spatial ability both received statistically significantly more positive responses in the 3D group compared to the control group. However, no difference was found for intelligibility for cataract surgery [61]. Similarly, the study by Morgulis et al. [56] that compared the use of existing online resources with a purpose-built, targeted eLearning module on leukaemia for medical students demonstrated an overwhelmingly positive response from students assigned to the targeted module.

Three (33%) studies [43,61,62] compared the effects of different eLearning modes on students' satisfaction. The study by Prinz et al. [61], earlier cited for favourable results of 3D over 2D learning of ophthalmic procedures on knowledge, reported greater student satisfaction with the 3D video. Although Hu et al.'s study [43] found that knowledge gain was higher for the 2D vs 3D learning group, enjoyment was higher in students assigned to 3D computer models. A study [62] which compared the effectiveness of a linear vs branched format for computer tutorials demonstrated that while the layout did not make a difference to their gain in ability, students in the linear group were slightly less likely to rate the tutorial as "valuable."

DISCUSSION

Our findings suggest that offline eLearning is at least equivalent, possibly superior to traditional learning in terms of students' knowledge, skills, and satisfaction and attitudes towards eLearning. Unfortunately, no studies evaluated impact on learners' professional attitudes towards patients. Eleven of the 33 studies testing knowledge gains found significantly higher gains in the eLearning intervention groups compared to traditional learning, whereas 21 did not detect significant differences or found mixed results. The remaining study did not test for differences. Eight of the 13 studies testing skill gains detected significantly higher gains in students allocated to the eLearning intervention, whilst 5 of the studies did not find statistically significant differences between the intervention and control group. Generally no differences in attitudes or preference of eLearning over traditional learning were observed, nor between different modes of offline eLearning.

Studies varied considerably in terms of type of eLearning (ie, full eLearning vs blended learning), the content, delivery channels, duration and frequency of exposure to the intervention, measures of outcomes, type of degrees, and seniority of students. For this reason, we did not calculate overall summary effect estimates. The majority of studies focused on full offline eLearning, whereas blended learning was used in fewer studies. Although the majority of studies comparing offline eLearning with traditional learning focused on seemingly similar offline eLearning programs, the extent of interaction they provided varied from a simple PDF file [51,54] on a PDA as a learning aid when learning how to do drug calculations [39] to software with quizzes and other interactive features [47]. The duration of exposure to the eLearning interventions and the time from completion of the eLearning intervention until knowledge or skills were measured ranged from 12 minutes [46] to 1

year [58]. The complexity of the eLearning modalities also varied. However, apart from 1 study that used a PDA with software that could function without the internet [39] all studies used computers.

The participants of the identified trials are representative of the intended population of students enrolled in undergraduate, health–related university degrees, and we expect that our results also apply to other similar university degrees. However, only 5 [49,51,60,65,69] of the 49 included studies were conducted in low– to middle–income countries, none of which in the Mediterranean and African regions. Because we focused on offline eLearning that does not require internet access, the limited availability of data from developing countries does not limit the scope of the review in terms of the technology studied. However, due to the fact that computer literacy and cultural factors may determine the overall effects of eLearning on all domains we studied, it is possible that our conclusions on effectiveness are not applicable to all countries and settings.

Over 50% of the studies [28,31,33,34,38,41–44,47,56, 57,62,63,67–69,71,75] asked students whether they would be keen to participate in a trial on eLearning. The resulting study participants are thus likely to be more eager to use the eLearning interventions, which might have resulted in more favorable assessment of this educational approach. Indeed, among the studies showing positive effects of eLearning, 4 studies [28,38,63,64] had a high risk and 6 studies [27,36,39,40,50,73] had an unclear risk of volunteer bias.

Our results are in line with the majority of the existing literature. A review on online eLearning that we prepared in parallel also showed that the effects of online eLearning were equivalent, possibly superior to traditional learning. Likewise, a systematic review of 12 RCTs on computeraided learning in dental education including both undergraduate students and dentists reported that statistically significant differences were not detected in the majority of studies comparing eLearning and traditional learning [21]. Another review of 12 randomized studies [20] concluded that the efficacy of computer-aided learning is reasonably well established. However, these authors also stressed that most of the included studies had methodological issues, eg, lack of power, attrition and a high risk of contamination. These methodological issues were still present in the studies we included in our review despite it being published a decade later.

There were also some differences between our results and the existing literature. Thirteen of the 14 included non– randomised controlled trials on the effect of computer– based instruction on knowledge and attitudes towards eLearning of health professions students favoured eLearning over traditional methods in another review [86]. Out of the 4 studies which compared students' attitudes towards the intervention, 3 demonstrated that computer-based instruction students had more positive attitudes towards their instructional method than students exposed to conventional teaching [86]. Our findings were less positive towards offline eLearning and generally showed no difference in knowledge and attitudes between the intervention groups. This might potentially be explained by a larger presence of studies that did not blind the outcome assessment in the aforementioned review [86]. This could have resulted in students feeling more obliged to answer positively. In addition, the review assessed the subjective outcomes of attitudes and satisfaction, the assessment of which was very heterogeneous in the included studies [86], whereas we only assessed the results regarding students' satisfaction and attitude that dealt with the difference between eLearning and traditional learning to keep the results as homogeneous as possible. Another systematic review [12] of 7 studies in allied health professions, medicine and nursing students reported that in all but 1 of the studies improvement in students' competencies, clinical skills, self-efficacy and clinical reasoning was seen when blended learning was used. This review included a very heterogeneous sample of studies with both online and offline blended learning. It included both controlled trials and trials that were not. Also, this review excluded all studies that did not report methods or results sufficiently or properly [12]. Our review yielded a less positive conclusion, perhaps because we considered all studies regardless of quality to assess the full body of evidence. Furthermore, we had a more comprehensive search strategy allowing us to review a much larger number of studies. Because of these differences and the differences in topic, it is therefore not surprising that we reached different conclusions.

Our study has many strengths. First, we optimised the probability of identification of all relevant literature by conducting our search using sensitive search strategy, multiple recognised literature databases without imposing language restrictions as well as by screening references of the selected articles. To enhance data quality, every identified article was screened by 2 people independently, and their results were compared. The same applied to the data extraction of the selected articles, which was enhanced by using a standardised form for recording. The distinction between undergraduate and postgraduate education, and the focus on the former, increased the applicability of our results. The learning process at postgraduate level tends to be different, involving bedside learning and more in-depth exploration of the content. Additionally, patient outcomes are usually used as a proxy measure of the effectiveness of educational interventions in postgraduate education. An additional strength of our report was that our search resulted in the

inclusion of both developed and developing countries. Finally, we followed the preferred reporting items for systematic reviews and meta–analyses (PRISMA), a framework tool used to set the minimum evidence–based items to be included when conducting and writing systematic reviews. Doing so and by using the Cochrane methodology maximized the completeness, transparency and accountability of our reporting of findings.

Despite its strengths, our systematic review also has some limitations. First, we were unable to identify unpublished studies. Second, we were unable to consider the pedagogical approach in more detail mainly because of the incomplete reporting of pedagogical methods within the included studies and because we did not request information on its details from the study authors. Third, our classification into offline eLearning and online eLearning and the other 3 categories is pragmatic and not an established classification. Other authors may suggest other groupings. However, eLearning remains a recent field in which the definitions, concepts, evaluation tools and measures still lack consensus [87]. Some of the studies categorised and analysed as offline eLearning were using eLearning interventions that were downloaded from WebCT Blackboard or sent to the students via email. This could be considered online eLearning, however, since the eLearning component could function fully offline and to avoid too much heterogeneity between the studies, we classified it as offline. Also, the mode of delivery of the eLearning material could have been replaced by an offline one (eg, CR-ROM) and could therefore be used in areas with limited internet access.

Finally, our choice to include articles from 2000 onwards only could be challenged. However the choice of 2000 can be justified by a rise in the interest in eLearning illustrated in part by several national and international reports and publications on the topic from this year onwards. These more recent reports are likely to have used more modern forms of eLearning than older reports and are thus timelier, especially considering technological developments.

Furthermore, there were some limitations to the evidence that was available and included in this review. The lack of or insufficient reporting of results in some of the included studies resulted in the restricted level of detail in the analysis of certain outcomes of interest. Another important limitation to the evidence included is the lack of clarity of 1 or more aspects of the methodology used in the majority of the included trials and in some cases the occurrence of attrition. Although we contacted authors to obtain the missing information, some authors did not reply to our request and others did not know the answers. The lack of or insufficient reporting of methods and results lead to an inability to draw a robust conclusion allowing for generalisation to all undergraduate students around the world due to the study selection process and the limitations of the included studies.

We were unable to assess the cost–effectiveness of eLearning vs traditional learning because none of the identified studies formally assessed it. The 6 articles [27,34,35,53, 68,70] that mentioned economic elements such as hours spent developing the program suggested that eLearning modules cost more to develop than using already established traditional learning methods, but also highlight that this can be done with limited resources.

None of the studies specifically addressed adverse effects of eLearning. This may be because potentially negative effects of eLearning that are regularly cited [24] focus on loneliness and depression, which could be regarded to be an aspect of students' satisfaction and attitudes. Potential reduced efficacy and effectiveness of eLearning would have been evaluated as part of the assessment of skills and knowledge.

In summary, the findings from this systematic review suggest that offline eLearning is similar to traditional learning in terms of knowledge and skill acquisition and that it is possibly superior to traditional learning. In addition, they offer a more convenient, and more cost—effective, alternative to facilitate competency development and the training of health care professionals around the globe.

Our results indicate that students were more favourable towards the eLearning interventions. However, due to a high risk of bias these results should be interpreted with caution.

Implications for policy makers

This systematic review indicates that offline eLearning is likely to be as effective as traditional learning, possibly superior and this presents a potential incentive for policy makers to encourage the development of offline eLearning curricula. These offline eLearning programs could potentially help address the health care worker shortage by contributing to greater access to education and training as part of scaling up the education of health workers especially in the developing world where internet access is limited and the need for an increase in the number of health professionals is greatest. However, there are still barriers (eg, computer access and access to eLearning material) that need to be overcome and this could be helped by changing policies and facilitating investments in ICT.

Implications for educational institutions

Many eLearning programs were developed by local enthusiasts within universities and this review showed that these programs were likely to be effective in terms of knowledge and skills acquisition. Therefore, educational institutions should encourage such enthusiasts who wish to develop eLearning materials to improve the learning experience and knowledge and skills acquired by their students. Despite the fact that a robust conclusion on whether or not eLearning is superior to traditional learning could not be drawn we believe that educational institutions should not refrain from investing in offline eLearning material.

Implications for future research

Offline eLearning is still likely to be a key player in education in the next decade where technology in education is expected to be used more and more and therefore researchers should continue to investigate the effects of this intervention on knowledge, skills and students' satisfaction and attitudes especially in developing countries. Future individual studies should continue to improve the methodology (eg, avoid contamination and volunteer bias) with which the eLearning intervention is investigated and report their study according to the CONSORT guidelines.

Furthermore, we suggest that a well–defined and commonly used taxonomy for the different types and aspects of eLearning should be developed and employed in future research to enable easier comparison of different eLearning studies.

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Online eLearning for undergraduates in health professions: A systematic review of the impact on knowledge, skills, attitudes and satisfaction

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A/Prof J Car 3 Fusionopolis Link #03–08Nexus@one–north Singapore 138543 josip.car@imperial.ac.uk **Background** Health systems worldwide are facing shortages in health professional workforce. Several studies have demonstrated the direct correlation between the availability of health workers, coverage of health services, and population health outcomes. To address this shortage, online eLearning is increasingly being adopted in health professionals' education. To inform policy–making, in online eLearning, we need to determine its effectiveness.

Methods We performed a systematic review of the effectiveness of online eLearning through a comprehensive search of the major databases for randomised controlled trials that compared online eLearning to traditional learning or alternative learning methods. The search period was from January 2000 to August 2013. We included articles which primarily focused on students' knowledge, skills, satisfaction and attitudes toward eLearning and cost-effectiveness and adverse effects as secondary outcomes. Two reviewers independently extracted data from the included studies. Due to significant heterogeneity among the included studies, we presented our results as a narrative synthesis.

Findings Fifty-nine studies, including 6750 students enrolled in medicine, dentistry, nursing, physical therapy and pharmacy studies, met the inclusion criteria. Twelve of the 50 studies testing knowledge gains found significantly higher gains in the online eLearning intervention groups compared to traditional learning, whereas 27 did not detect significant differences or found mixed results. Eleven studies did not test for differences. Six studies detected significantly higher skill gains in the online eLearning intervention groups, whilst 3 other studies testing skill gains did not detect differences between groups and 1 study showed mixed results. Twelve studies tested students' attitudes, of which 8 studies showed no differences in attitudes or preferences for online eLearning. Students' satisfaction was measured in 29 studies, 4 studies showed higher satisfaction for online eLearning and 20 studies showed no difference in satisfaction between online eLearning and traditional learning. Risk of bias was high for several of the included studies.

Conclusion The current evidence base suggests that online eLearning is equivalent, possibly superior to traditional learning. These findings present a potential incentive for policy makers to cautiously encourage its adoption, while respecting the heterogeneity among the studies. service [2]. At this juncture; the WHO estimates a shortage of 7.2 million doctors, nurses, midwives and other health care professionals worldwide [3]. Addressing this shortfall in health care professionals through training requires a substantial investment.
Meanwhile, the Internet and the development of information technologies have revitalized the exchange of information and training worldwide. Consequently, eLearning is used increasingly in medical and health professional education, to tackle the global shortage of health workers. eLearning is "an approach to teaching and learning, representing all or part of the educational model applied, that is based on the use of electronic media and devices as tools for improving access to training, communication and in-

Health care workers are central to any health system; their

activities are aimed at enhancing the health of the commu-

nity, nation or region in general. However, these professionals are distributed unevenly across the globe; countries with

lower relative need have the highest numbers of health

workers, while those with the greatest burden of disease

have a much smaller health workforce. The health worker crisis is at its worst in sub–Saharan Africa and Asia. Inci-

dentally, countries in this region are facing a double burden

of both infectious and non-communicable diseases [1],

and they lack the funds, technology, infrastructure and trained health workers needed to provide basic health care

based on the use of electronic media and devices as tools for improving access to training, communication and interaction and that facilitates the adoption of new ways of understanding and developing learning" [4]. It does not only differ from traditional learning (ie, face–to–face learning that takes place in a classroom environment) in the medium by which learning is delivered [5], but also affects the teaching and learning approaches used. eLearning can take the form of a full eLearning approach, which is entirely driven by technology, or be a mix of the traditional and fully computer–based methodologies (blended learning). Blended learning might be more suitable for health care training because of the need to combine hands–on skills– based training at a practical level as well as self–directed learning [6–10].

Lately, eLearning has started to make way into the developing countries and is believed to have huge potential for governments struggling to meet a growing demand for education while facing an escalating shortage of teachers [11]. However, in both the developing and non–developing countries, network connectivity and bandwidth availability are the key obstacles to the effective delivery of online eLearning [5,12]. Despite this, eLearning presents many opportunities for universities, including the reduction of the delivery costs [13], increased scalability [14], improved access and availability by removing geographical and temporal barriers and allowing access to relevant experts and novel curricula [15]. Online eLearning represents a further evolution of computer–assisted or computer based or offline eLearning and is an important tool in medical training and may transform the way medicine is taught [16]. In the recent years, nearly all medical schools in the USA and Canada employ online course materials [17]. eLearning could be full or blended, full eLearning can be distributed geographically and/or temporally, and communication between student and teacher is handled electronically. This manuscript focuses on online eLearning; systematic review of offline eLearning is published in a parallel article [18].

Online eLearning approaches varied widely in configuration (tutorial, asynchronous discussion, live conferencing, etc.), instructional methods (eg, practice exercises, cognitive interactivity) and presentation [17]. The majority of reviews of effectiveness of online eLearning included observational studies with several methodological deficiencies [16,17,19–22]. This systematic review aims to evaluate the effectiveness of online eLearning from randomised controlled trials conducted among undergraduate health professionals, specifically looking at its impact on students' knowledge, skills, attitudes and satisfaction.

METHODS

We conducted a systematic review following the Cochrane methodology [23].

Search methods for identification of studies

Electronic searches. We limited our electronic searches to records published on or after the year 2000 in order to highlight recent developments. We developed a search strategy for MEDLINE (OvidSP) using a combination of keywords and MeSH terms that captured the types of intervention and the types of participants under evaluation in this systematic review (Table 1). We adapted the search strategy for use in EMBASE (OvidSP), PsycINFO (Ovid SP), Cochrane Central Register of Controlled Trials (CEN-TRAL), Web of Science, and Educational Resources Information Center (ERIC) (ProQuest). Where available, we used validated methodological filters to limit our searches to Randomised Controlled Trials (RCTs) and cluster RCTs (cRCTs). We ran the searches in August 2013.

Searching other resources. We checked reference lists of the included studies and systematic reviews of the literature identified by our electronic searches for additional studies.

Inclusion criteria

Types of studies and participants. We included studies published in any language on students of (i) undergraduate, health–related university degrees; or (ii) basic, health–

Table 1. Search strategy for use in MEDLINE (Ovid SP)*

IUNIC	• Search shalegy for use in MEDLINE (Ovid SL)
1.	exp Education, Distance/
2.	educat\$.mp.
3.	learn\$.mp.
4.	train\$.mp.
5.	instruct\$.mp.
6.	2 or 3 or 4 or 5
7.	"computer assisted".mp.
8.	Internet.mp
9.	distance.mp.
10.	
11.	online.mp.
12.	virtual.mp.
13.	"mobile phone".mp.
14.	"cell\$ phone".mp.
15.	smartphone
16.	smart–phone
17.	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18.	6 adj3 17
19.	exp Computer–Assisted Instruction/
20.	eLearning.mp.
21.	e–Learning.mp.
22.	mLearning.mp.
23.	m–Learning.mp.
24.	"virtual learning environment".mp.
25.	1 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26.	exp Education, Medical, Undergraduate/
27.	exp Education, Nursing/
	exp Medical Staff/
29.	exp Physicians/
30.	doctor?.mp.
31.	
32.	
33.	exp Nurses/
34.	
35.	exp Nurses' Aides/
36.	exp Allied Health Personnel/
37.	exp Community Health Workers/
38.	exp Health Personnel/
39.	exp Health Manpower/
40.	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
	or 37 or 38 or 39
41.	25 and 40
42.	Randomized controlled trial.pt.
43.	
44.	Randomized.ab.
45.	Placebo.ab.
46.	Drug therapy.fs.
47.	Randomly.ab.
48.	Trial.ab.
49.	Groups.ab.
50.	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51.	exp animals/ not humans.sh.
52.	50 not 51
53.	41 and 52
<u> </u>	Limit 53 to yr="2000 –Current"Correspondence to:
21.	Line 55 to 31 - 2000 -Current Correspondence to.

*Source: Ovid MEDLINE® In_process& Other Non–Indexed Citations and Ovid MEDLINE® 1946 to Present. Date of search: 16 August 2013, 09:53. Limits: Year – 2000. Filter: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity–maximizing version (2008 revision); Ovid format.

related vocational training programmes. We defined undergraduate education or basic vocational training as any type of study leading to a qualification that: (i) is recognised by the relevant governmental or professional bodies of the country where the studies were conducted; and (ii) entitles the qualification–holder to apply for entry level positions in the health care workforce. For this reason, graduate medical education courses from the USA were included.

We considered studies on candidates for and holders of the qualifications listed in the Health Field of Education and Training of the International Standard Classification of Education (ISCED–F) [24], except studies on students of traditional and complementary medicine. We hence included students reading dental studies, medicine, nursing and midwifery, medical diagnostic and treatment technology, therapy and rehabilitation, or pharmacy. Medicine and dentistry were classified under the umbrella term *allied health professions*.

Types of intervention. First, we conducted a systematic mapping of the types of technologies used by the included studies to deliver the learning materials, through which we identified 6 broad categories of eLearning interventions, based on the technologies employed: (1) Offline computer–based eLearning, (2) Online and local area network–based eLearning, (3) Psychomotor skills trainer, (4) Virtual reality environments, (5) Digital game–based learning and (6) mLearning. We allocated each included study to the category that fitted the study best. Please refer to **Online Supplementary Document** for a definition of these categories.

We only included studies in which online eLearning interventions were used to deliver the learning content, studies were categorized as online eLearning if the delivery of the learning content was done through the internet or intranet connections. Only studies that compared online eLearning or blended eLearning methods to: (i) traditional learning, (ii) an alternative eLearning or blended learning method; or (iii) no intervention was eligible for inclusion. These studies could either be studies where eLearning was the sole means by which the intervention was delivered or where eLearning was part of a complex, multi–component intervention.

Types of outcome measures. To be eligible for inclusion, studies had to report at least 1 of the following primary or secondary outcomes.

Primary outcomes: (1) Students' knowledge, measured using any validated or non–validated instrument (eg, pre– and post–test scores, grades, perceived knowledge survey scores); (2) Students' skills, measured using any validated or non–validated instrument (eg, pre– and post–test scores, time to perform a procedure, number of errors made whilst performing a procedure, perceived up–skilling); (3) Students' satisfaction and attitudes towards eLearning, measured using any validated or non–validated instrument (eg, self–efficacy, satisfaction, acceptability).

Secondary outcomes: (1) Health economic properties of the interventions (eg, implementation cost, return on investment); (2) Adverse and/or unintended effects of eLearning (eg, potential feelings of depression and loneliness, dropout risks [25] and "computer anxiety" [26]).

We only considered studies to have measured students' satisfaction and attitudes towards eLearning if they met all of the following criteria: (i) they compared the differences between intervention and control groups for these outcomes; (ii) the content of the survey questionnaires related to the teaching method (ie, eLearning method, blended learning, or traditional learning); and (iii) the adjectives used in the survey questionnaires accurately described attitudes and/ or satisfaction.

Study selection and data collection

The study selection process is summarised in the PRISMA flow diagram (Figure 1). In brief, we screened the titles and abstracts of the citations identified by our electronic and manual searches to identify potentially relevant studies, of which we assessed the full-text report to ensure they meet the inclusion criteria we specified. Review authors completed these tasks independently and met to compare their results and reach consensus.

Every selected study was allocated to a pair of review authors, with 10 review authors participating in total. Each review author independently extracted data from the included studies using the structured data extraction sheet shown in **Online Supplementary Document**.

Each pair of reviewers compared their completed data extraction forms and any discrepancies between review authors' results were resolved through discussion; if no agreement could be reached, a third review author acted as an

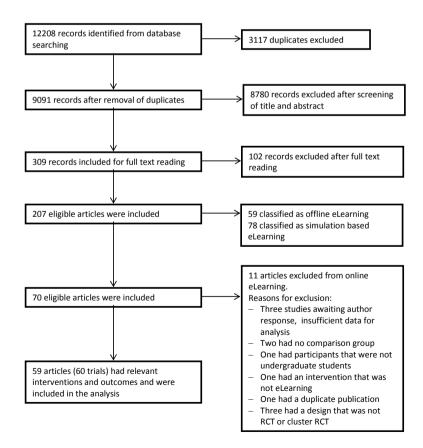


Figure 1. Flowchart of the studies included in the review.

arbiter. Because 10 review authors participated in the data extraction process, some categories were interpreted differently by some reviewers. Therefore, 3 reviewers went over the entire data extraction again to ensure uniformity.

We contacted authors of studies containing incomplete data to request the missing information. Some authors did not reply to our request for additional information, whilst other authors did not know the answer to our questions. For 1 study the response obtained from the author resulted in the subsequent exclusion of the study from the systematic review.

Assessment of risk of bias in included studies

During the data extraction process, we assessed the risk of bias at the outcome level using tools recommended by the Cochrane Collaboration [23]. For RCTs, we did so across the domains of (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other bias including the comparability of intervention and control group; characteristics at baseline; validation of outcome assessment tools; reliability of outcome measures; and protection against contamination.

> We assessed the risk of bias for cRCTs across the domains of (1) recruitment bias, (2) baseline imbalances, (3) loss of clusters and (4) incorrect analysis. For each study, 2 reviewers independently categorised each domain as low, high or unclear risk of bias.

Summarising the data

We qualitatively compared the characteristics of the participants and of the interventions between the included studies to determine the feasibility of conducting a meta–analysis. Because of substantial clinical, educational, content and methodological heterogeneity we did not conduct a meta–analysis. Instead, we adopted a thematic summary approach [27].

RESULTS

12 208 reports were identified from database screening of which 309 were retrieved for full-text evaluation of which 207 studies met the inclusion criteria (Figure 1). Fifty-nine articles [25–82] complied with the term internet and local area network or online eLearning (see **Online Supplementary Document** for detailed description) and were included in the

analysis. One study [83] involved students in 2 consecutive RCTs that were analysed separately (Ainsworth 2012A, Ainsworth 2012B). Thus the total number of evaluated trials was 60.

Included studies

All studies were published in peer reviewed journals between 2000 and 2013 except 1 dissertation [81]. All included studies were parallel RCTs or cRCTs. The included number of RCTs and cRCTs suggests an increase in the number of publications after 2007 as eighteen of the included studies (30%) have been published between 2000 up and 2007 (ie, 8 years). The remaining 42 studies (70%) have been published in the shorter time interval between 2008 and mid 2013 (ie, 5.5 years). Out of all 60 included studies, 33 studies investigated eLearning in the field of medicine [26,28,32,34-36,38-41,44,45,49,50,54,58-62,64-70,72,75,77,78,80,82]. Eleven of the articles [25,2 7,33,42,43,53,56,74,76,79,83] were exclusively from nursing, 3 [55,57,81] were within the field of physical therapy, whereas 3 other studies within pharmacy [30,31,71]. Nine studies [29,37,46-48,51,63,73] investigated eLearning for dentistry students. Additionally, 1 article [52] dealt with medicine, nursing, and physical therapy while the remaining study recruited university students, but did not define their discipline [81].

Participant characteristics

The total number of participants included across all trials was 6750 participants. The study with the smallest control group had 10 participants [77] whereas the largest control group had 249 participants [55]. The study with the smallest intervention group had 10 participants [33], while the largest intervention group had 349 participants [55]. Most studies were conducted among undergraduate university students apart from 9 studies [27,29–31,33,42,53,54,79] that investigated the effect of network–based eLearning for vocational training. Out of the 20 (33%) studies [30,32,33,40,45,47–49,52,53,55,57,64,65,71,73,75, 76,83] that specified the age of the students, the lowest mean age of participants in a control group was 20.0 years [55] and the oldest was 30.0 years [76]. The lowest mean age in an intervention group was 19.9 years [75] and the highest was 30.0 years [76].

Intervention characteristics

Fifty studies compared eLearning to traditional learning, and 10 studies [26,35,36,45,46,61–63,66,74] compared 1 mode of eLearning to another mode of eLearning. The duration of exposure ranged from 9.05 minutes to 9 months [83]. Most of the studies (51 out of 60,85%) were conducted exclusively in high income countries. Seven studies were conducted solely in low– to middle–income countries: 2 in Brazil [25,26]; 2 in China [38,56]; 1 in Thailand [33]; and 2 in the Chinese Taipei [27,42]. One study [52] was conducted simultaneously in Brazil and the USA (Figure 2).

The majority of the studies used a website to present the learning material to the participants as part of their intervention [25–34,37–46,48–66,68–80,82,83]. Three studies [35,36,47] used a spaced education intervention, ie, an intervention in which the educational exposures are spaced and repeated over time [35]. In these studies the learning material was presented via email on a regular basis [35,36,

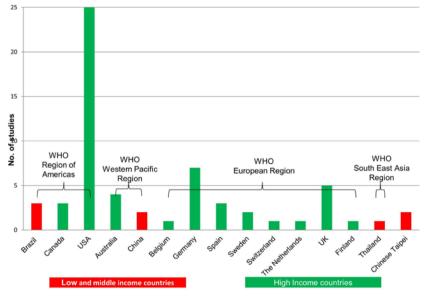


Figure 2. Country of origin of included, examined studies for low– and middle–income and high income countries separately.

47]. One study used video conference lectures as an intervention [67], and 1 study used a visual concept map [81].

Primary outcomes

Students' knowledge assessment. The knowledge gained from the exposure to the intervention was assessed in a number of different ways in the included studies. Overall, 53 [25–27,29–33,35–46,48–52,54,56–67,69,70,72–83] out of the 60 studies looked at a knowledge as an outcome. Nineteen of these studies [25,32,35,40,43,45,48–50,56, 57,60,69,72,74,75,77,80,82] used only multiple choice questions (MCQs) to test students' knowledge and understanding. Six studies used MCQs as a knowledge assessment tool together with an adaptive spaced test [36], gap text questions [51], matching and short answer questions [61], open ended and true/false questions [64], short essay questions [81] and a key features test [59].

Seven studies reported using test questions [31,39,40,44,67, 70,78] to assess knowledge of study participants. Six other studies used open ended [30,33,63,66] or Likert type questionnaires [29] or even "fill in the blank" questions [73]. The rest of the studies measured students' knowledge gain via other testing means including general numeracy tests [83]; written exams [41,46,58,65]; independent observers' assessment [79]; cognitive assessment instruments [54]; surgical knowledge test scores [76]; a Diagnostic Thinking Inventory and individual students' performance in solving clinical reasoning problems [38]; a modified version of the Dartmouth Sleep Knowledge and Attitudes survey [62]; an interactive evaluation about melanoma [26]; an orthodontic examination form for each patient [37]; or some form of a knowledge assessment scale or checklist [42,52,68].

Students' skills assessment. Skills were evaluated in 16 studies [28–30,32–34,39,42,53,55,57,63,68,69,71,72] using various methods to assess the outcome. Nine studies [33,34,42,55,63,68,71,72] used a rating scale and/or checklists (eg, an OSCE) to assess clinical skills. One study [53] used a search skills test, another 1 [29] a Likert type questionnaire while 3 studies evaluated students skills through written assessments such as data collection sheets [30], written case analysis [41] and open questions on standardised tasks [32]. Finally, 1 study [28] measured the degree of new skills acquisition by using a self–assessment report whilst another [39] measured the time that students made to complete the assigned exercise.

Students' satisfaction and attitudes towards eLearning.

Feedback from students assessed as their attitude towards the eLearning intervention was reported as an outcome in a total of 14 studies [28,29,32,33,43,45,48,49,54–56,63, 64,72]. In all of these, students' attitude was measured by questionnaires. Student satisfaction was considered as an outcome in 33 studies [25,32–34,37–41,43,46–48,50–52,55,57–61,64– 66,68,69,73–76,80,82]. Seventeen of these studies [33,34,38,40,51,52,55,57,59,61,64–66,68,73,75,76] mentioned that student satisfaction was evaluated with Likert scale questionnaires. The 16 remaining studies comparing student satisfaction among the students [25,32,37,39, 41,43,46–48,50,58,60,69,74,80,82] used different types of questionnaires or surveys without mentioning the use of Likert scales.

Secondary outcomes

Cost–effectiveness of the eLearning interventions. Cost–effectiveness or cost–benefit or cost–utility of eLearning interventions were not assessed in any of the studies, however, some of the studies mentioned several financial and resource related elements of eLearning.

Buzzell et al. [54] mentioned that in the future many experts would be involved in content generation for their respective disciplines and that content could be shared online among their disciplines. Thus the online content development and delivery would not need the involvement of many faculty at all stages of content development and in turn educational institutions would be cost efficient. Stain et al. [67] mentioned that the costs of setting up videoconferencing were comparable to the costs of live lectures after an initial hardware investment of less than US\$10000. Stewart et al. [68] cited a paper saying that reduction of instructor training time, labour costs and institutional infrastructure could result in significant cost-efficiency. Toumas et al. [71] mentioned in the discussion that using the Internet leads to "reduced costs in terms of tutor-led workshops and is more efficient, enabling more complex topics to be covered in workshops". Hauer et al. [34] deduced that the video cases were cheaper than the mini-CPX (Clinical Performance Evaluation) examination they used. An in-person examination of a class of 150 students cost approximately US\$ 5400, which did not yet include Clinical Skills Centre maintenance costs, costs of case development and payment of Centre staff. In contrast, plain technologies as video cases were produced at a total cost of US\$ 2200. Besides, the video cases could be reused freely, whereas the in-person mini-CPX requires annual purchase of a license.

In contrast, Fleming et al. [73] mentioned that the development of web-based or Computer Assisted Instruction is expensive in terms of time and energy spent. Phadtare et al. [52] made a general comment on the potential lack of necessary infrastructure and "new" costs associated with online courses.

Adverse and/or unintended effects of eLearning. Adverse or unintended events of the eLearning intervention were not reported in any of the studies.

Excluded studies

Initially, 65 studies were categorised as online eLearning studies. We reclassified 2 studies [84,85] as non-networked computer-based because their eLearning interventions could be fully functional even without network technologies' support. Three studies [86-88] were excluded because of insufficient data while another [35] was excluded as a duplicate paper. Seven studies [89–95] were excluded during the data extraction process, just before the analysis, because they met 1 or more of the exclusion criteria. Four of these 7 studies [91,92,94,95] were excluded because their study design was not a parallel or cRCT eg, a cross-over design [94]. Two studies [89,93] were excluded because they did not include comparison groups for the eLearning intervention eg, 2 different blended teaching methods using a common eLearning intervention in exactly the same way [93]. Finally, 1 study [90] used an eLearning intervention which was considered ineligible for our study ie, electronic voting during the lecture [90].

Risk of bias in the included parallel RCTs

Thirty-one of the studies were considered to be at high risk of bias. [25,33,34,36,38-41,44,49-51,53,55,57,60,62-64,69,70,72,74-77,79-81,83]. Twenty-nine of the studies [26,30,32,35,43,48,52,54,56,59,61,65-67,73,78] had 1 or more categories classified as an unclear risk of bias, especially regarding the allocation of participants to intervention groups. There was only 1 study [47] with all the categories classified as low risk of bias (Figure 3 and 4). Risk of bias is described in detail in the Online Supplementary Document.

Effects of online eLearning interventions

The 60 randomized trials included in our review assessed the effectiveness of online eLearning interventions in terms of knowledge, skills, attitudes and satisfaction. The findings were based on comparisons between online eLearning and traditional learning or between various modes of online eLearning. A study may have compared more than 1

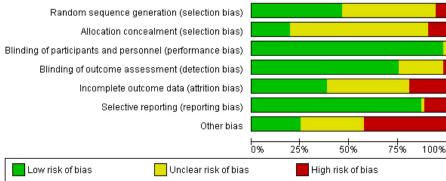


Figure 3. Overall risk of bias graph.

Figure 4. Risk of bias for each individual parallel randomised controlled trial (RCT) separately.	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ainsworth 2012a(83)	ŭ.	₩ •	•		- -	ő	ة
Ainsworth 20124[83] Ainsworth 2012b[83]	•	•	•	•	•	-	?
Answorth 20120(83) Arroyo-Morales 2012(57)	•	?	•	?	•	•	-
Beeckman 2008[79]	•	• ?	•	•	-	•	?
Brettle 2013[53]	•	?		?	-	•	?
Buzzell 2002[54]	?	?	•	•	?	•	•
Chao 2003[26]	?	?	•	•	•	•	?
Chen 2007[81]	•	•	•		?	•	
C-Villanueva 2012[55]	•	?	•	•	?	•	
Erickson 2003[30]	•	?	•	•	•	•	?
Fernandez 2011[76]	?	?	•	•		•	
Fleming 2003[73]	•	?	•	•	?	•	?
Friedi 2006(32)	?	?	•	•	•	•	?
Frith 2003[74]	?	•	•	•	•	•	
Gerdprasert 2011[33]	?	?	•	?	•	•	?
Hauer 2009(34)	?	?	•	?	•	•	•
Jenkins 2008[78]	•	?	•	•	•	•	?
Juliani 2011(25)	•	•	•	•	?	•	•
Kandasamy 2009(80)	•	•	•	•	•	•	?
Kerfoot 2008(35)	?	?	•	•	•	•	?
Kenoot 2010[36]	?	?	•	•	?	•	•
Komolpis 2002[37]	?	?	٠	•	٠	٠	٠
Lee 2010[38]	•	?	•	•	•	•	•
Leong 2003(39)	•	?	•	?	•	•	Θ
Lewis 2011[40]	•	•	•	•	?	•	•
Lipman 2001[41]	?	?	•	•	•	•	?
Maag 2004[43]	?	?	•	•	•	•	•
Mahnken 2011[44]	•	•	•	•	?	•	•
Mattheos 2004[46]	•	?	•	•	•	•	?
Nkenke 2012[47]	?	?	?	?			
Nkenke 2012a(48) Ochoa 2008(49)	•	•	•	•	•	•	-
Octioa 2008(49) Palmer 2008(50)	•	•	•	?	?	•	-
Peroz 2009[51]	2	•	•	•	• ?	•	
Phadtare 2009[52]	•	•	•	?	?	•	?
Raupach 2009(59)	?	?	•	•	•	•	•
Raupach 2010[60]	?	?	•	•	•	•	•
Ricks 2008[77]	•	?	•	•	•	?	•
Romanov 2006[61]	?	?	•	•	?	•	•
Salas 2013[62]	?	?	٠	•	?	•	•
Schittek 2005[63]	?	?	÷	•	?	٠	•
Smits 2012[64]	٠	?	•	?	•	•	•
Spickard 2002[65]	•	•	•	•	?	•	•
Spickard 2004[66]	?	?	•	•	•	•	•
Stain 2005[67]	?	?	•	?	?	•	?
Stewart 2013[68]	•	•	•	•	?	•	?
Stoiz 2012(69) 50% 75% 100% Subramanian 2012(70)	•	?	•	?	?	•	•
	?	?	•	•		•	?
sk of bias Succar 2010[82]	?	?	•	•	?	•	•
Truncali 2011[72]	?	2	•	?	2	•	
Wang 2009(56) Yeung 2012(75)	•	? •	•	•	?	•	-
reung 2012[/5]	-	-	•	•	•	•	-

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outcome between groups, and each outcome may have been assessed in multiple ways. For example, a study which compared students' acquisition of skills may have assessed skills in terms of the student's performance on a global rating scale, the ability to perform a specific procedure, as well as the ability to comply with the requirements in a checklist. As a result, the number of comparisons made across studies for a particular outcome may exceed the number of studies which reported on that outcome. Only 2 studies [32,33] measured all specified outcomes of knowledge, skills, attitudes and satisfaction.

The studies were split into 2 research themes evaluating the impact of eLearning interventions for undergraduate health care education: traditional learning vs online eLearning, and online eLearning vs online eLearning.

Traditional learning vs online eLearning

Fifty of the 60 included studies (83%) compared online eLearning with traditional learning. [25,27–34,37–44,47–58,60,64,65,67–73,75–83]. Table 2 presents the summary of the findings of the individual studies. Further description of the nature of the interventions is in the **Online Supplementary Document**.

Students' knowledge. Amongst the 60 studies which compared online eLearning with traditional learning, knowledge was assessed in 43 RCT studies (86%) [25,27,29–31,37–44,48–52,54,56–60,64,65,67,69,70,72,73,75–83] and 7 cRCT studies [27–29,31,42,58,71].

Twelve studies (27%) assessing knowledge gain demonstrated significantly higher knowledge gains for students assigned to the online eLearning compared to those exposed to traditional learning [31,41,49,51,52,56,60,70,72, 77,79,83]. Outcome measures for these studies were based on test items or questions [31,70], written case analyses [41], MCQs [50,51,56,60,72,77], the Six-subgroup Quality Scale (SSQS) [52], a general numeracy test [83] and independent assessments by evaluators [79]. The sample size of these studies ranged from 39 to 1475. Six of these 12 studies were conducted on medical students [41,49,60,70, 72,77], 3 among nursing students [56,79,83], 1 among dentistry students [51], 1 among pharmacy students [31], while 1 study [52] was conducted among medicine, nursing, and physical therapy students. Five of these studies used full online eLearning as the main intervention [49,52, 70,77,79] whereas 7 used blended learning [31,41,51,56,60, 72,83].

Post–intervention knowledge was not significantly different between eLearning and traditional learning in 24 (48%) of the included studies [25,32,33,37,38,42–44,48,50,54, 57–59,64,65,69,73,75,76,78,81,83]. Three studies [27,30, 39] showed mixed results ie, favouring the intervention, control or neither 1 depending on the specific indicator of knowledge being assessed. In 1 (2%) study [82] knowledge was assessed but not tested for statistically significant differences between the intervention groups.

Finally, there were 3 studies [29,30,80] that demonstrated significantly higher knowledge gains for students assigned to traditional eLearning compared to those exposed to online eLearning. Two of these studies [29,80] used full online eLearning as the main intervention while the other 1 [40] used blended learning.

Students' skills. Overall, 15 studies – 11 RCTs [30,32–34,39,53,55,57,68,69,72] and 4 cRCTs [28,29,42,71] measured skills as outcome.

Of the studies that evaluated differences in skill acquisition, 6 (40%) found significantly greater skill acquisition amongst students assigned to online eLearning [33,34,42,57,71,72]. The number of participants included in these studies ranged from 44 to 303. Two of these studies were conducted in medical students [34,72], 2 in nursing students [33,42], 1 in physiotherapy students [57] and 1 in pharmacy students [71]. Four of these studies used traditional learning as their main intervention [34,42,57,71], whereas 2 used blended learning as the main intervention [33,72].

Three studies (21%) did not detect a significant difference in skill acquisition between groups [39,53,55]. One study [30] showed mixed results ie, favouring the online eLearning or the traditional learning group depending on the specific indicator of skills being assessed. This study had 3 groups, comparing pharmacy students' knowledge and ability to assess metered–dose inhaler (MDI) after a lecture based tutorial, a web–based tutorial and being provided no teaching on the topic at all. Finally, there was 1 study [69] that demonstrated significantly higher skill gains for students assigned to traditional learning compared to those exposed to online eLearning. This study used full eLearning as the main intervention.

Students' attitudes and satisfaction. Twelve studies (24%) – 10 RCTs [32,33,43,48,49,54–56,64,69,72] and 2 cRCTs [28,29] – assessed attitudes as an outcome of the intervention through questionnaires.

Eight of these studies [29,32,33,43,49,50,54,56] (67%) did not find a statistically significant difference between the 2 types of learning methods, or the study showed mixed results for online eLearning vs traditional learning depending on the test evaluated. Three studies [28,55,72] assessed attitude, but did not test for statistically significant differences between the intervention groups. None of the studies reported a significant result on student attitudes favouring online eLearning interventions.

The remaining study (8%) [64] reported more positive attitudes towards the intervention in the traditional learning groups. This study used full online eLearning as the main intervention. PAPERS

Study	DISCIPLINE	KNOWLEDGE	Skills	Attitude	SATISFAC-		INTERVENTION DELIVERY APPROACH	Characteristics
Ainsworth 2011a [83]	Nursing	NS			TION	PARTICIPAN	15	
Ainsworth 2011b [83]	0	E						
Arroyo–Morales 2012 [57]		NS	E		NS	46	Blended learning	IG: Online tutorial (ECOFISIO) CG: Self–study
Baumlin 2000 [58]	Medicine	NS			NS	100	Blended learning	IG: Computer Assisted Instructions (EMCyber–School) CG: Lectures
Beeckman 2007[79]	Nursing	E				426	Full eLearning	IG: 1 h eLearning program CG: 1 h lecture
Brettle 2013 [53]	Nursing		NS			77	Full eLearning	IG: Online tutorial CG: 1 h face–to–face tutorial
Buzzell 2002 [54]	Medicine	NS		NS		34	IG1: Full eLearning IG2: Blended learning	IG: Web–based tutorials IG2: Traditional lectures with web– based tutorials CG: Traditional lectures
Cantarero2012 [55]	Physiotherapy		NS	DNT	DNT	50	Full eLearning	IG: Online materials CG: access to books and documents
Chen 2007 [81]	Undefined	NS				145	IG1: Full eLearning IG2: Traditional learning	IG1: A visual advance organizer IG2: Text outline CG: Textbook reading without an advance organizer (AO)
Chen 2012 [27]	Nursing	М				146	Blended learning	IG: Online tests CG: Group A: Paper references, Group B: No assistance
Cox 2008 [28]	Medicine		DNT	DNT		138	IG1: Traditional learning IG2: Blended learning	IG1: Group discussion IG2: Website, Videos CG: Paper based, traditional learnin materials
DeBate 2013 [29]	Dentistry	Т	DNT	NS		608	Full eLearning	IG: Online (computer and website) CG: Regular curriculum
Erickson 2003 [30]	Pharmacy	М	М			42	IG1: Traditional learning IG2: Full eLearning	IG1: Lecture–based tutorial IG2: Web–based tutorial CG: No intervention
Fernandez 2011[76]	Nursing	NS			NS	116	Full eLearning	IG: Computer assisted learning CG: Face-to-Face lecture
Fleming 2003 [73]	Dentistry	NS			NS	31	eLearning and traditional learning separately	IG: Slide/audiotape self-instruction and web-based self-instruction CG: Web-based self-instruction and slide/audiotape self-instruction
Flowers 2010 [31]	Pharmacy	E				79	Blended learning	IG: Web–based Multimedia Vignette CG: No Web–based Multimedia Vignettes
Friedl 2006 [32]	Medicine	NS	DNT	NS	NS	126	Full eLearning	IG: online multimedia course CG: Text books
Gerdprasert 2010 [33]	Nursing	NS	E	NS	NS	84	Blended eLearning	IG: Web, interactive graphics, animation CG: Traditional teaching
Hauer 2013 [34]	Medicine		E		Е	303	IG1: Full eLearning IG2: Traditional learning	IG: Web based module CG: Group work, role play.
Jenkins 2008 [78]	Medicine	NS				73	Blended learning	IG: Internet–based tutorial CG: Lecture.
Juliani 2011[25]	Nursing	NS			DNT	80	Full eLearning	IG: Designing a schedule with internet CG: Designing a schedule without internet
Kandasamy 2009 [80]	Medicine	Т			NS	62	Full eLearning	IG: Online CAI module CG: Review articles (Text based)
Komolpis 2002 [37]	Dentistry	NS			NS	99	Full eLearning	IG: Digital records on PC CG: Hardcopy records
Lee 2010 [38]	Medicine	NS			NS	52	Blended learning	IG: Web–based problems, workshop

Medicine

Μ

NS

Leong 2003 [39]

54 vs

325*

IGI: Full eLearning

IG2: Full eLearning

NS

IG1: Computer based cases (other

IG2: Computer based cases (C1+C2) CG: No Computer based cases

CG: No workshop

than C1+C2)

Study	DISCIPLINE	Knowled	ge Skills	ATTITUDE	SATISFAC- TION	No. of participant	INTERVENTION DELIVERY APPROACH	CHARACTERISTICS
Lewis 2011 [40]	Medicine	Т			NS	39	Blended learning	IG: Web-based MCQ's
Lipman 2001[41]	Medicine	E			NS	130	Blended learning	CG: Textbook resource IG: Website, books
								CG: Books, discussions
Lu 2009 [42]	Nursing	NS	E			147	Blended learning	IG: Lectures and interactive web-
								based course
M 2004[42]	NI	NIC		NS	NIC	06	IC1. Traditional la consista	CG: lectures only
Maag 2004[43]	Nursing	NS		INS	NS	96	IG1: Traditional learning IG2: Blended learning	IG1: Text and image
							IG2: Blended learning	IG2: Text and image and animation IG3: Text, Image, Animation, and
							IG5. Diended learning	Interactivity
								CG: Text modules
Mahnekn 2010[44]	Medicine	NS				96	IG1: Blended learning	IG1: eLearning, self
inamierar zo ro [, , j	methemic	110				20	IG2: Blended learning	IG2: eLearning, mandatory
							102. Dichaed learning	CG: No access to eLearning
Nkenke 2012 [48]	Dentistry	NS		NS	NS	42	Blended learning	IG: Technology enhanced learning
)						0	CG: Didactic lectures, PowerPoint
								presentation
Nkenke 2012[47]	Dentistry				NS	42	Blended learning	IG: Spaced education
	-							CG: Lectures
Ochoa 2008 [49]	Medicine	Е		NS			Full eLearning	IG: Web-based interactive program
								CG: Traditional text.
Palmer 2008 [50]	Medicine	NS			DNT	130	IG1: Traditional learning	IG1: Written case–studies
							IG2: Blended learning	IG2: Clinical material + interactive
							IG3: Blended learning	computer-based case studies
								IG3: Clinical material + interactive
D 2000 [51]	D. et a				216		DI 1 11 ·	computer-based case studies
Peroz 2009 [51]	Dentistry	E			NS	85	Blended learning	IG: Online education CG: PowerPoint, discussions
Phadtare2009 [52]	Medicine;	E			E	48	Full eLearning	IG: Online materials
1 Haddare 2009 [92]	Nursing;	L			L	10	i un cicarning	CG: Off–line materials
	Physiotherap	W						ee. on mic materials
Raupach 2009 [59]	Medicine	NS			DNT	148	Blended learning	IG: Web–based teaching module
1							0	CG: face-to-face traditional lecture
Raupach 2010 [60]	Medicine	Е			E	74	Blended learning	IG: Web-based module
								CG: Traditional lecture
Ricks 2008 [77]	Medicine	Е				23	Full eLearning	IG: Computer Assisted Learning
								group
								CG: No intervention
Smits 2012 [64]	Medicine	NS		Т	NS	128	Full eLearning	IG: Case based eLearning
1 . 1							- 11	CG: Text based learning
Spikard 2002 [65]	Medicine	NS			E	95	Full eLearning	IG: Online lecture
Ct. 1. 2005 [67]	N 1	NIC				12 00	чт 11 т ·	CG: Traditional learning
Stain 2005 [67]	Medicine	NS				12 VS 98	* Full eLearning	IG: Videoconference lectures CG: Conventional lectures
Stewart 2013 [68]	Medicine		DNT		NS	71	Blended learning	IG: Online access to learning conter
Stewart 2015 [00]	Wiedicille		DINI		113	/ 1	biended learning	CG: Standard content
Stolz 2012 [69]	Medicine	NS	Т		Т	129	Full eLearning	IG: Web–based training
	method	0	-		-		B	CG: Lectures
Subramanian 2012	Medicine	Е				33	Full eLearning	IG: Interactive medical software
[70]							0	CG: Lectures
Succar 2010 [82]	Medicine	DNT			NS	147	Blended learning	IG: Computer based training
								CG: Traditional teaching
Toumas 2009 [71]	Pharmacy		Е			236	Blended learning	IG: Internet–based Tutorial
								CG: Small group workshop
Truncali 2011 [72]	Medicine	Е	Е	DNT		141	Blended learning	IG: Web-based Tutorial
								CG: Lectures
Wang 2009 [56]	Nursing	E		NS		133	Blended learning	IG: Online, self–learning
								CG: Traditional multimedia lecture
Yeung 2013 [75]	Medicine	NS			NS	78	Blended learning	IG: Computer–assisted learning
								CG: Text–/image–based learning

E – Results favoured online eLearning over traditional learning, NS – No significant difference between online eLearning and traditional learning, MCQ – Multiple choice questions M – Mixed results, T – Results favoured traditional learning over online eLearning, DNT – Difference not tested, CG – Control group, IG – Intervention group

*Average number students exposed to videoconference lectures and conventional lectures, respectively.

Out of 29 studies looking at the level of student satisfaction, 4 [34,52,60,65] (14%) found a significantly greater proportion of students exposed to online eLearning who were satisfied compared to those exposed to traditional learning. One of these 4 studies [60] compared blended learning with traditional learning, whilst the other 3 [34,52,65] used full eLearning interventions compared with traditional learning ones. Twenty studies (74%) did not detect any significant difference [32,33,37–41,43,47,48,51,57,58,64,68,74– 76,80,82] while in 4 studies satisfaction was assessed [25,50,55,59] but not tested for statistically significant differences between the intervention groups.

There was 1 study [69] using full online eLearning as the main intervention that reported a statistically significant better student satisfaction in the traditional learning group.

Comparison of different types of eLearning against each other

Ten (18%) of the included studies [26,35,36,45,46,61–63,66,74] compared the effectiveness of various modes of online eLearning against each other. Eight of these studies [26,35,45,46,61–63,74] compared groups of eLearning with different levels of student interaction. In 2 of them "interactivity" was also facilitated by collaborative tools, ie, online web chats [74] and discussion forums and online message systems [61].

Students' knowledge. All of the 10 studies [26,35,36,45,46, 61–63,66,74] comparing various forms of online eLearning measured and reported their effects on knowledge.

Five studies observed a difference in results between different modalities of eLearning. In a study comparing an adaptive form of spaced education against a linear, repetitive one [36], the adaptive eLearning intervention showed better results than its "passive" form. Another study showing significant knowledge acquisition for an "active" eLearning intervention was Chao et al [26] where a linear educational environment (website) supported by complementary information (skin anatomy images) which users could access at will was compared to a non modified website. Similarly, in 1 study [63] an eLearning intervention, allowing students to play a video back and forth at their will showed better knowledge gains in comparison to an eLearning intervention where the procedure was linear. In a study [61] on a "passive" type of eLearning, offering course material through conventional World Wide Web technology and by letting students engage with the instructor only by email resulted in higher knowledge gains in comparison to an interactive eLearning intervention where

students could make use of all the learning tools of the Web CT (online proprietary virtual learning environment system) [61]. A "passive" eLearning intervention showed favourable results also for Salas et al [62]. In this study, participants in the "passive" eLearning group were solely provided with a list of random sleep facts and trivia presented in a PowerPoint format. The "active" eLearning intervention consisted of an online, self–paced, sleep medicine learning module.

Non statistical significant differences were found in 4 studies [35,45,66,74] comparing different online eLearning modalities. One study showed no difference in knowledge acquisition between eLearning modes [46].

Students' skills. Skill acquisition was assessed in 1 study [63]. This study showed no significant differences in skills acquisition between the 2 different (active vs passive) eLearning modalities.

Students' attitudes and satisfaction. Manikam et al. [45] and Schittek Janda et al. [63] were the only studies amongst the 10 studies comparing different eLearning modalities that assessed attitude. The study by Manikam et al showed no difference in students' attitudes between the 2 eLearning modes. In this study a dummy learning package was compared to the ABD learning package, ie, symptom–based decision–making pathways software. Schittek Janda et al. reported no significant differences in skills acquisition between the 2 different (active vs passive) eLearning modalities.

Four (40%) studies [46,61,66,74] compared the effects of different eLearning modes on student satisfaction. Two studies [46,61] showed no difference in students' satisfaction for the 2 eLearning modes. Frith et al. [74] reported that students in the group that used collaboratively a 6–week Web–based course on cardiac rhythm interpretation supported by online chat software were more satisfied than students in the group who worked on the same course independently. In the study by Spickard et al. [66] students in the groups of the online lecture of power point slide presentation with audio narration.

DISCUSSION

Summary of main results

This systematic review reports on the effectiveness of online eLearning for undergraduates in health professions. We found that online eLearning does lead to changes in knowledge, skills, attitude and satisfaction and seems to be more effective than traditional learning in terms of knowledge and skills gained. Our findings are similar to previous reviews of online eLearning [21,22,96–100] and offline eLearning [18]. In our review, 29% of the studies showed significantly higher knowledge gains, 40% of the studies showed significantly greater skill acquisition, 67% of the studies showed no difference in attitude and 14% of the studies showed higher satisfaction with online eLearning than traditional learning. The participants in the included studies were from the fields of medicine, dentistry, pharmacy or medical allied studies enrolled at universities, with a smaller number conducted at vocational training centres or colleges. Consequently, the results of this systematic review apply to students from similar disciplines, universities and colleges. The majority of the studies were conducted in high-income countries with exception of few [25,26,33, 38,42,52,56,101] which were from low to middle income countries, hence these results are generalizable only to their corresponding settings.

The studies included in our review had a high degree of methodological, educational and clinical heterogeneity, similar to previous reports [21,22,96-100]. Knowledge assessment was, for example, conducted using different test items or questions [31,70], written case analyses [41], MCQs [49,51,56,60,72,77] the Six-subgroup Quality Scale (SSQS) [52], a general numeracy test [83] and independent assessments. Similarly, there was variability in the assessment of skills, attitudes and satisfaction across the studies. Hence pooling of effect estimates was not possible. Mode of online interventions varied across the studies, most of the studies used a website, while some used other interventions such as spaced education, video lectures or visual concept map. Furthermore, there were great variations in exposure time to the eLearning intervention. Financial and resource related elements of eLearning was reported only in 8 studies [34,52,54,59,67,68,71,73]. Nevertheless, none of the studies included a robust costeffectiveness analysis of eLearning vs traditional learning and therefore it is not possible to provide an assessment on cost-effectiveness of online eLearning. Furthermore, no studies reported on the adverse effects of online eLearning.

The overall quality of evidence included in this systematic review is not uniform and contains a significant number of studies with methodological weaknesses with only 1 high quality study [48]; similar findings were reported in previous reviews. [16,19,20,22,102,103] Most of the included studies did not adhere to the CONSORT guidelines for reporting of RCTs [104] and thus their risk of bias was unclear. Several of the included studies had high risk of bias due to volunteer [49,51,57,60,72,74,83] and attrition bias. [34,41,70,72,79]. Due to the weaknesses of most of the included studies a strong conclusion on whether there is a clear difference between online eLearning and traditional learning effectiveness that applies to the general population of learners cannot be drawn.

Our study has many strengths. The review was based on a thorough search of available literature which identified a large number of potentially eligible studies identified and synthesized by a multi-disciplinary international team and it offers a number of advantages over previous work in this area. The key strength is an attempt to combine breadth of scope in terms of widely defining eLearning and the range of health professions covered. The review encompasses all empirical studies (RCTs). To ensure data quality, article screening and data extraction was done independently by 2 persons to avoid subjective bias, disagreements were resolved through discussion. The review included studies from both developed and developing countries and thus provides crucial information on the usage, effectiveness and applicability of online eLearning in these settings. Finally, the review used standard methods for systematic reviews and meta-analyses in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) which makes it transparent.

The review had a few limitations. The included studies had several methodological rudiments, we contacted the authors to obtain necessary information for assessing the risk of bias for these studies, however due to time constraints, and it was not possible to contact all authors. Moreover, due to the lack of a uniform, standardized terminology for eLearning studies, we categorized studies as online eLearning (ie, local area network or web–based) and offline eLearning (ie, non–networked or computer based). Although we assigned each individual study to only 1 category, it is important to highlight that there might be some degree of overlap between categories as 1 form of technology may be built on another one.

In summary, this systematic review compares online eLearning and traditional learning in undergraduate health– related students and consolidates current knowledge on the effectiveness of online eLearning. The evidence from the highest and the lowest quality studies indicates that online eLearning is equivalent to and perhaps even more effective than traditional learning in terms of knowledge and skills gained. The generalization of these findings is limited only to the studied population in the review.

Online learning's ubiquity provides a convenient and possibly a more cost–effective alternative to traditional learning and has great potential in supporting health care workforce capacity building and competency development globally. This review highlights the need for improvements in the methodological design in future studies.

Implications for policy makers

The findings of this review present a potential incentive for policy makers to encourage adoption and the development of online eLearning programs. These online eLearning programs could be useful in training health care professionals in countries with acute health care worker shortage, without substantial investments. These online technologies if adopted earlier could help lower the burden of diseases by increasing the health care professional per capita. Though adoption of these online technologies would involve some initial start—up cost, it would be largely beneficial as the potential for the return on investment is high in terms of health gains and lives saved.

Implications for educational institutions

Online eLearning offers many opportunities. This review shows that eLearning is as effective as the traditional learning and with many advantages compared to traditional learning. The universities could adopt these technologies and could reach out to a wider audience within and outside their country, thus offering a tremendous growth opportunity for the educational institutions. Institutions could employ online eLearning to train their health workforce without having to spend for their travel elsewhere within or outside their countries.

Implications for future research

The findings of the review have many implications for research. Future evaluations of online eLearning should aim to answer many remaining research questions from intervention design features to setting or modality for online eLearning, and build cost–effectiveness models. We should especially aim to strengthen the evidence base for developing countries.

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The effectiveness of mHealth interventions for maternal, newborn and child health in low– and middle–income countries: Protocol for a systematic review and meta–analysis

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Dr Claudia Pagliari eHealth Research Group Centre for Population Health Sciences The University of Edinburgh Medical School Doorway 3 Teviot Place Edinburgh EH8 9AG, Scotland, UK claudia.pagliari@ed.ac.uk Introduction Rates of maternal, newborn and child (MNCH) mortality and morbidity are vastly greater in low- than in high-income countries and represent a major source of global health inequity. A host of systemic, economic, geopolitical and sociocultural factors have been implicated. Mobile information and communication technologies hold potential to ameliorate several of these challenges by supporting coordinated and evidence-based care, facilitating community based health services and enabling citizens to access health information and support. mHealth has attracted considerable attention as a means of supporting maternal, newborn and child health in developing countries and research to assess the impacts of mHealth interventions is increasing. While a number of expert reviews have attempted to summarise this literature, there remains a need for a fully systematic review employing gold standard methods of evidence capture, critical appraisal and meta-analysis, in order to comprehensively map, quality assess and synthesise this body of knowledge.

Objectives To undertake a systematic review and meta–analysis of studies evaluating the impacts of mobile technology–enabled interventions designed to support maternal, newborn and child health in low– and middle–income countries.

Methods 16 online international electronic databases of published scientific abstracts and citations will be interrogated for the period 1990 to 2014 (no language restrictions) in order to identify relevant studies. Ongoing/unpublished studies will be identified through searching international trial repositories and consulting experts in the field. Study quality will be assessed using appropriate critical appraisal tools; including the Cochrane Handbook's 7 evaluation domains for randomised and clinical trials, the Cochrane Effective Practice and Organisation of Care (EPOC) guidelines for other comparative study types, and the Effective Public Health Practice Project (EPHPP) quality assessment tools for observational studies. Blinded assessment by at least two reviewers, with arbitration by a third if necessary, will ensure rigour. Meta–analysis will be undertaken, where possible, using a random–effects model. Sensitivity and subgroup analyses will be reported. Publication bias will be assessed.

Ethics and dissemination Ethical approval is not required.

Results These will be presented in one manuscript. The review protocol is registered with the International Prospective Register for Systematic Reviews (PROSPERO) CRD42014008939. PROTOCOLS

Nowhere are global inequalities more starkly evident than in maternal, newborn and child health. For every 100 000 births in low income countries around 240 women die, compared with only 16 in high income countries, while a child is approximately 18 times more likely to die before the age of five years [1]. Although considerable progress has been made in meeting Millennium Development Goals 4 and 5 there remains a substantial gap between these aspirations and reality [2].

Preventable birth complications such as haemorrhage, obstructed labour and infection, which are exacerbated by poor pre– and post–natal care, account for a substantial proportion of these deaths [3,4]. These complications can also result in significant long–term health consequences for mothers, such as obstetric fistula, uterine prolapse, incontinence, depression, chronic infections and infertility, as well as mental or physical disability in their offspring [5,6].

While pathogens clearly play an important role, this excessive mortality and morbidity has been attributed largely to endemic failures in health and social care systems in low and middle income countries (LMIC) [3], set against a context of societal challenges such as lack of education and knowledge, delays in help seeking and poor nutrition. These factors are often exacerbated by gender discrimination, ethnic and religious division, and a lack of a social and political voice, as well as the more obvious economic and demographic barriers [2,7,8].

The problems described above have been compounded by historically weak information systems and poorly integrated infrastructures in LMIC [9]. However, the increasing penetration of mobile networks into these regions is opening up new opportunities to enable coordinated, accessible, safe, effective and citizen-centric health care. mHealth, or mobile health, refers to the use of wireless, portable information and communication technologies (ICT) to support health and health care [10]. The concept of mHealth remains somewhat poorly defined in the literature, although useful taxonomies are beginning to emerge [11]. It may be thought of as involving various devices such as cell- and smart-phones, personal digital assistants, tablet computers, laptops and digital point-of-care testing devices, *delivery modes* such as voice, text, images, or video, and applications such as public health messaging, personalised behaviour change interventions, workflow management, health surveillance, access to patient records, clinical decision support, education, diagnostics and remote care provision. Thus mHealth solutions may be configured to support patients, professionals and health systems. Although mHealth has attributes in common with 'telemedicine' and 'telehealth' (enabling care at a distance) and other areas of 'health informatics' (eg, via digital records) the term is reserved exclusively for mobile and wireless digital tools and interventions.

Although the area of mHealth is relatively young, it has attracted considerable attention from, and investment by, donors, the private sector and development agencies as a means of alleviating a range of global health challenges. Among them, maternal, newborn and child health are key priorities, along with the monitoring and management of HIV and other infectious diseases. International collaborations such as the mHealth Alliance and development agencies like USAID are increasingly documenting experiences of mHealth implementation projects in this area, one of the best known being MAMA (Mobile Alliance for Maternal Action), a patient messaging system that has been implemented in several LMIC [12,13] While the significance of mHealth is understood, evidence of its potential value and impact on maternal, newborn and child health is less clear. Intermediate outcomes, such as improved antenatal attendance through the use of SMS appointment reminders [14], are increasingly being reported, although evidence of impacts on maternal and child mortality and morbidity rates is rarer [15]. Significantly, the recent World Health Organisation guideline on postnatal care of the mother and newborn identifies a need to evaluate the potential role of mHealth in improving patient outcomes [16].

To date, the majority of mHealth implementation projects in LMIC have tended to be small-scale, donor-funded initiatives, which have taken place without the benefit of an adequate evidence-base, and have not themselves been configured with research in mind. However the area is beginning to attract greater research attention and funding, with a growing body of studies examining the appropriate design of mHealth interventions for patients and professionals, their impacts on the processes and outcomes of care, and the barriers and facilitators to scaling up [14,15]. Challenges include the difficulties of undertaking rigorous trials in projects driven by development or policy goals, attributing cause and effect where both interventions and the environments in which they are delivered are complex, and designing and targeting interventions for greatest impact. For example, a recent trial of text-messaging to encourage attendance at antenatal care suggested improved uptake of preventive care services but the authors acknowledge that randomisation at the level of health facilities rather than individual patients may have failed to capture women at earlier stages of pregnancy, for whom community-based recruitment might have been more appropriate [11]. Reviewers such as Tomlinson et al have also stressed the importance of adapting tools to suit the context and culture of care in order to optimise their likely impacts [15].

A number of systematic reviews on the topic of mHealth exist but these are not ideally suited to establishing impacts on MCNH outcomes in LMIC, in some cases due to the absence of certain databases likely to capture research from these regions [17,18] or because they are concerned more with methodological and process issues than patient out-

comes [19]. The majority of secondary literature specific to mHealth for MCNH in LMIC consists of broad expert reviews summarising activities and aspirations and descriptive case studies illustrating how mobile technologies are being used to support the strengthening of health systems [20-22]. Although these provide valuable insights, many are vision-driven rather than evidence-seeking and the influence of the mobile telecommunications industry can be hard to disentangle. A project to map the state of the evidence on mHealth and MCNH was recently undertaken by Philbrick for the mHealth Alliance [22]. This converged a literature review with a landscape scan of existing projects and interviews with key respondents to provide a breakdown of studies in this area, their limitations and their implications for research and policy. While the report is useful, the mixed-methods 'gap analysis' exercise was not configured as a formal systematic review and is thus likely to have missed important sources of evidence and steps in the critical appraisal of study methodology, which would be expected in a classic systematic review. Two other quasisystematic literature reviews addressed the topic using basic search terms and a subset of six databases [23,24]. A systematic review project selected for funding by the Alliance for Health Policy and Systems Research in 2011 [25] remains unpublished, as is the case for a systematic review undertaken for a Master's degree project at the University of Edinburgh, which focused only on SMS messaging for prenatal care [26]. We are therefore confident that there is a clear need for a new systematic review employing gold standard methods of evidence capture, critical appraisal and meta-analysis, in order to comprehensively map, quality assess and synthesize existing evidence of the impact of mobile technology-enabled interventions on maternal, newborn and child health in low and middle income countries. The current study will follow the rigorous methods advocated by the International Cochrane Collaboration in order to achieve these aims and the findings will be interpreted with reference to relevant theoretical and policy perspectives, in order to derive recommendations for research and practice. In this protocol we describe the steps that are planned in order to undertake this systematic review.

DESIGN

This is the protocol for a systematic review and meta–analysis of the literature.

AIMS AND OBJECTIVES

To undertake a systematic review and meta–analysis of studies evaluating the impacts of mobile technology–enabled interventions designed to support maternal, newborn and child health in low– and middle–income countries.

INCLUSION AND EXCLUSION CRITERIA

Included interventions

We are interested in any intervention delivered using mobile ICT, which is designed to support the health of pregnant women and their unborn children, women during and after childbirth, newborns, infants and children up to five years and the national, state, city, or community level in an LMIC setting.

Mobile ICT refers to portable, wireless digital devices usually (although not exclusively) supported by networked mobile or satellite communications infrastructures, such as cell-phones, smart-phones, satellite phones, personal digital assistants, enterprise digital assistants, tablet computers, laptops, portable media players and gaming consoles, Radio Frequency Identification Device (RFID) tags, Global Positioning System (GPS) trackers and digital diagnostic devices [27]. mHealth interventions involve a range of delivery modes such as voice calling, Voice over Internet Protocol (VoIP), text messaging via Short Message Service (SMS), transfer of still or moving images via Multimedia Message Service (MMS), multimedia downloads, or live video [17]. Within the scope of this review we include all applications of these technologies for directly supporting MCNH patients - such as public health messaging, personalised behaviour change communications, self-care information and remote care provision, as well as interventions designed to enable trained or lay health workers to provide better care to patients - such as electronic medical records or care plans for supporting individualised care; decision support tools for informing screening or intervention decisions, workflow planning applications, clinical documentation tools, global positioning tools for patient tracking and portable point-of-care testing devices able to transmit data via mobile phone or satellite networks.

Included study types

The following study designs will be potentially eligible for inclusion:

- Randomised controlled trials (RCTs, quasi–RCTs, Controlled Clinical Trials – CCTs). Study designs included by The Cochrane Effectiveness Practice and Organisational Care (EPOC) group – (controlled before–and–after studies, interrupted time series studies),
- Cohort and case-control studies.

Types of participants included

The following types of participant will be potentially eligible for inclusion:

- Pregnant women,
- Women in ante-natal, intra-natal and postnatal periods,
- Newborns,

- Children aged 0–5 years,
- Health workers through which an intervention aimed at improving the health of the above groups is mediated.

Excluded interventions

This review will exclude interventions focused on reproductive health (eg, promotion of HPV vaccination), sexual health (eg, domestic violence reporting) or sexually transmitted diseases (eg, antiretroviral treatment (ART) compliance reminders), unless pregnant women or mothers of newborns or children 0–5 years are specifically targeted (many pregnant women in LMIC have HIV).

mHealth interventions aimed at managerial or financial aspects of health systems (such as stock control or accounting) will not be included in this review.

Studies describing physically 'mobile' clinics or services will be excluded unless mobile ICT is a fundamental medium through which the service is delivered.

Excluded study types

The following study types will be excluded:

- Studies undertaken in high income countries,
- Expert opinion,
- Descriptive case studies and case series,
- Technical reports and reviews.

Types of participants excluded

The following types of participants will be excluded:

- Men, adolescent males and boys over the age of 5 years,
- Women, adolescent females and girls over the age of 5 years who are not pregnant, have not recently given birth or are not caring for their child aged 0–5,
- Facility managers and government decision makers not directly involved in the care of patients. (mHealth interventions such as clinical dashboards may support higher–level administrative functions associated with the operation of MCNH services but do so indirectly).

Types of comparisons

Included studies will be those comparing the mHealth intervention with usual care, another intervention or a non– exposed control group.

Types of outcome measures

The following outcome measures will be included:

- Primary outcomes: all outcome measures indicative of maternal mortality; maternal morbidity; newborn and child morbidity,
- Secondary outcomes: number of planned antenatal and post natal visits; number of unscheduled care visits and emergency care incidents; quality of life; quality of care (delivery by skilled birth attendants, appropriate use of

evidence–based medical and obstetric interventions where available); self–efficacy; cost–effectiveness; immunisation cover; child developmental milestones and mHealth intervention–related adverse events.

SEARCH METHODS

Eligible study reports will be identified from the following sources:

- The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register), MED-LINE, EMBASE, CINAHL, PsycINFO, AMED, Global Health, TRIP, ISI Web of Science (Science and Social Science Index), WHO Global Health Library, IndMed, Pak-MediNet, KoreaMed, NHS Health Technology Assessment Database, African Index Medicus (encompassed in the WHO Global Health Library), and POPLINE. Studies will be identified using subject headings appropriate to each database as well as free-text terms. In addition, reference lists of articles of interest and citations to included articles will be screened for additional eligible published studies.
- Unpublished and in progress studies will be identified from the following trial registries: www.clinicaltrials.gov; www.controlled-trials.com; www.anzctr.org.au; http:// www.who.int/ictrp/en/.
- Expert consultation.

The search strategy is presented in detail in Tables 1 and 2.

Restrictions include:

- Time span: 1990–2014. (Rationale: the first mobile–health technology interventions started in the early 1990s) [20].
- Language: none (for foreign language papers translations will be sought)
- Countries identified as low or medium income according to the United Nations Human Development Report released in March 2013 [28]. We are aware that the position of countries in such indices changes over time and will note the date of the articles. We will also include articles referred to using the generic terms used by other authors to describe LMIC (eg, developing country, emerging economy) [29,30].

STUDY SELECTION

Each author will be assigned one or more databases to search using an appropriately adapted version of the strategy described above (mindful of database differences). Retrieved titles and abstracts will be collated and distributed to pairs of authors for independent screening in order to identify potentially eligible studies. Disagreement will be resolved by consensus, or arbitration involving a third author where necessary. Full text articles will be retrieved for selected studies, and two authors will assess whether each of these meets the set inclusion criteria. Disagreement will

Table 1. Search strategy: Medline format

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1. (eHealth or e–Health).mp.
2. (mHealth or m–health or mobile health).mp.
3. Telemedicine/ or (telecare or telehealth care or mobile telehealth
care or mobile telemedicine or mCare or m-care).mp.
4. apps or mobile applications/
5. (mobile communication or mobile technology or mobile devic*).mp.
6. Computers, Handheld/ or Microcomputers/ or (tablet computers
or mobile tablet computers or mobile technolog*).mp.
7. Communication satellite.mp.
8. Cellular phone/ or (cellular phone* or cell phone or mobile
phone).mp.
9. MP3 player*.mp.
10. Text Messaging/ or (texting or text messag* or messag* or text* or
short message or SMS or multimedia technol* or multimedia
messag* or multi–media messag*).mp.
11. (Personal digital assistant* or PDA).mp.
12. (Smartphone or smart–phone).mp.
13. (podcast* or pod–cast*).mp.
14. Social media/ or Social networking/ or (Twitter or Facebook).mp.
15. (Global positioning system or GPS).mp.
16. Radio Frequency Identification Device/ or RFID.mp.
17. or/1–16
18. Pregnancy/ or Pregnant women/ or Pregnancy outcome/
19. Parturition/ or childbirth.mp.
20. Obstetrics/
21. Maternal Health Services/ or matern*
22. (pregnan* or maternal or maternal health).mp.
23. Labor, or Labour or Obstetric/
24. Delivery, Obstetric/
25. Midwifery/ or Traditional Birth Attendant.mp.
26. Postpartum period/ or puerperium.mp.
27. Delayed delivery.mp. or three delays.mp.
28. Pregnancy complications/ or Obstetric Labor complications/ or
Obstetric Labor, Premature/ or Puerperal Disorders/ or Depres-
sion, Postpartum/ or Maternal Mortality/
29. Infant, Newborn/ or neonat*.mp.
30. Prenatal Care/ or Perinatal Care/ or Postnatal Care.mp.
31. (Antenatal care or intrapartum care or postpartum care or
post–partum care or puerperal care).mp.
32. (Perinatal complication* or postnatal complication*).mp.
33. Birth injuries/
34. Breastfeeding/ or (breastfeeding or breast–feeding).mp.
35. or/18–34
36. Intervention studies/ or experimental studies.mp.
37. analytical stud*.mp.
38. Clinical trial/ or Controlled Clinical Trial/ or Randomized
Controlled Trial/ or (clinical trial or controlled clinical trial or
randomized
controlled trial).mp.
39. Double–Blind Method/ or Single–Blind Method/ or (double–blind
design or single–blind design).mp.
40. Placebos/ or Random Allocation/ or random*.mp.
41. (Controlled before and after stud*).mp.
42. Interrupted time series.mp.
43. Cohort studies/ or (cohort stud* or cohort).mp.
44. (control or healthy control).mp.
45. Case-control studies/ or case-control stud*.mp.
46. or/36–45
47. 17 and 35 and 46
48. limit 47 to yr="1990–2014"
49. limit 48 to human

be resolved by discussion amongst reviewers, with referral to a third author if necessary. Reasons for exclusion of studies will be noted. All authors will discuss and agree the refined list of included studies.

QUALITY ASSESSMENT AND ANALYSIS

The assessment and documentation of the methodological quality of included controlled trials will follow the Cochrane approach using the methods detailed in section eight of the Cochrane Handbook for Systematic Reviews of

Table 2. Search strategy: free-field format

(mHealth or m–Health or eHealth or e–Health or telemedicine or mobile health or mobile telehealth care or mobile phone or cellular phone or personal digital assistant or mobile tablet computers or smart phone or mobile technology or apps or mobile applications or text messag* or short messag* or SMS or multimedia messag*)

AND

(child* or infant* or baby or babies or neonatal or newborn* or preterm* or prematur* or pregnan* or pregnant women or mother* or obstetric labor or obstetric labour or obstetric delivery or obstetric labor complications or midwifery or traditional birth attendant or perinatal care or prenatal care or antenatal care or intrapartum care or postnatal care or perinatal complications or postnatal complications) AND

(analytical stud* or epidemiologic* or compar* or evaluat* or followup or follow up or prospective or retrospective observation* or cohort or case-control or trial* or RCT or controlled before and after study or interrupted time series or intervention* or prospective or retrospective or control* or double-blind or single-blind or random*)

Interventions [31]. Intervention studies will be assessed using the Cochrane Effectiveness and Practice Organisation of Care (EPOC) guidelines [32,33]. The following seven parameters will be used to assess trial quality: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other biases. Each parameter of trial quality will be graded: A – low risk of bias; B – moderate risk of bias; C – high risk of bias and an overall assessment for each controlled trial using the same three criteria will be made. Observational studies will be similarly assessed using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies [34]. Reviewers will not be masked to study details. Agreement of reviewers on methodological quality assessment will be assessed and disagreements will be resolved by discussion.

All assessments of study quality will be performed by at least two reviewers (UN, CP) with any disagreement resolved by consensus, or arbitration via a separate reviewer where necessary.

DATA EXTRACTION

Two reviewers will independently extract data using customised data extraction forms. The following information will be extracted:

- Author and year,
- National affiliation of author and funding source,
- Country in which the study took place,
- Study design,
- Healthcare setting,
- Target users,
- Type of mHealth intervention device; delivery mode; application type; stated purpose of intervention; theoretical basis if specified,
- Range of outcome measures described maternal mortality and morbidity, newborn and child mortality and

morbidity, emergency care, quality of life, quality of care (delivery by skilled birth attendants, appropriate use of evidence–based medical and obstetric interventions where available), immunisation rates, and cost–effectiveness of interventions,

• Key findings from each included study will be summarised and tabulated.

DATA ANALYSIS

Data will be presented in tabular and narrative form. Where possible, meta-analyses will be performed on methodologically comparable studies (comparable particularly with regards to the study design, type of ICT and endpoint measures studied and assessment methods of these) reporting main, primary, and secondary outcomes. The meta-analysis results will be presented in forest plots. The choice of statistical tests will depend on the nature of the outcome variable. Application of either a fixed effect or random effects model will be dependent on the degree of heterogeneity. Heterogeneity will be assessed both qualitatively and quantitatively using I² statistic. Where possible, adjusted effect estimates will be pooled in meta-analyses using generic inverse-variance analysis. Point estimates and 95% confidence intervals will be reported for all analyses. Sensitivity analyses will be performed in subgroups of study quality and of design characteristics (eg, randomised vs non-randomised; prospective vs retrospective). Where relevant data are missing, we will contact authors to request these. In addition, will undertake appropriate sensitivity analyses to address the different scenarios of missingness to be observed by making appropriate assumptions of each missing scenario. Finally, we will provide relevant discussion of the influence of missing data on the observed findings.

Where the number of included studies per outcome is sufficient, publication bias will be assessed visually through Funnel plots and tested by Egger's regression test [35] and Begg's rank correlation test [36].

ETHICS AND DISSEMINATION

Ethical issues

As only previously published studies are included and reported in the review, no additional formal ethical assessment and no informed consent is required.

Publication plan

The systematic review protocol is registered with the International Prospective Register of Systematic Reviews (PROS-PERO) CRD42014008939 (http://www.crd.york.ac.uk/prospero). Findings will be summarised in a single manuscript.

Timeline

Start date: 6 January 2014 Finishing date: 30 June 2014 Reporting date 30 June 2014

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Contributors: CP conceived the study; CP and UBN prepared the initial protocol draft. UBN, CP and LG were involved in study design, protocol and manuscript development. UBN and CP designed the search strategy. CP, LG, UBN, BIN, SHL and MM reviewed and refined the protocol and search strategy. All authors read and approved the final version of the manuscript.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje. org/coi_disclosure.pdf (available on request from the corresponding author). The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 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: The Mission Statement	1
EDITORIAL	Igor Rudan, Harry Campbell, Ana Marušić The first three years of the <i>Journal of Global Health</i> : Assessing the impact	2
110		
NEWS	Regions Agencies Resources	7–12 13–18 19–24
VIEWPOINTS	Xiangcheng Wang, Tao Sun China's engagement in global health governance: A critical analysis of China's assistance to the health sector of Africa?	25
VIE	Amelia Martin, Nathan Post, Martha Martin Syria: What should health care professionals do? Vijay Krishnamoorthy, Monica S. Vavilala, Charles N. Mock	29
	The need for ventilators in the developing world: An opportunity to improve care and save lives Asad Moten, Daniel Schafer, Paul Farmer, Jim Kim, Mauro Ferrari	32
	Redefining global health priorities: Improving cancer care in developing settingsa	36
PAPERS	Paul J. Krezanoski, Alexander C. Tsai, Davidson H. Hamer, Alison B. Comfort, David R. Bangsberg Household malaria knowledge and its association with bednet ownership in settings without large–scale distribution programs: Evidence from rural Madagascar Annie Lo, Dora Polšek, Simrita Sidhu	41
	Estimating the burden of neural tube defects in low– and middle–income countriesa Paul Mee, Mark A. Collinson, Sangeetha Madhavan, Elisabeth Dowling Root, Stephen M. Tollman, Peter Byass, Kathleen Kahn	50
	 Evidence for localised HIV related micro–epidemics associated with the decentralised provision of antiretroviral treatment in rural South Afr a spatio–temporal analysis of changing mortality patterns (2007–2010) Arsalan Cheema, Davies Adeloye, Simrita Sidhu, Devi Sridhar, Kit Yee Chan Urbanization and prevalence of type 2 diabetes in Southern Asia: 	59
	A systematic analysis Kristine Rasmussen, José Marcano Belisario, Petra A Wark, Joseph Antonio Mol Stewart Lee Loong, Ziva Cotic, Nikos Papachristou, Eva Riboli–Sasco, Lorainne Tudor Car, Eve Marie Musulanov, Holger Kunz1, Yanfeng Zhang, Pradeep Paul C Bee Hoon Heng, Erica Lynette Wheeler, Najeeb Al Shorbaji, Igor Svab, Rifat Atu Azeem Majeed, Josip Car	George,
	 Offline eLearning for undergraduates in health professions: A systematic review of the impact on knowledge, skills, attitudes and satisfaction Pradeep Paul George, Nikos Papachristou, José Marcano Belisario, Wei Wang, Petra A Wark, Ziva Cotic, Kristine Rasmussen, René Sluiter, Eva Riboli–Sasco, Lorainne Tudor Car, Eve Marie Musulanov, Joseph Antonio Molina, Bee Hoon H Yanfeng Zhang, Erica Lynette Wheeler, Najeeb Al Shorbaji, Azeem Majeed, Josi 	9(leng,
	Online eLearning for undergraduates in health professions: A systematic review of the impact on knowledge, skills, attitudes and satisfactione	108
ROTOCOLS	Ulugbek B. Nurmatov, Siew H. Lee, Bright I. Nwaru, Mome Mukherjee, Liz Grant, Claudia Pagliari The effectiveness of mHealth interventions for maternal, newborn and child health in low- and middle-income countries: Protocol for a	
oro	systematic review and meta–analysise	125

