

International Health Lecture 2014

Introduction

This is a summary of the Academy of Medical Sciences' 2014 International Health Lecture entitled '*A scientist, an engineer, and a banker walk into a pub...the not-so-funny truth about innovation in global health*' that was delivered by **Dr Trevor Mundel, President of the Bill and Melinda Gates Foundation's Global Health Program**, at the Academy on Monday 7 April 2014.

Lecture summary

This lecture summary may be read alone or alongside the slides from the lecture, which are available to download as a PDF on the Academy's website. The numbers on the right hand side of the following pages indicate which slides the commentary corresponds to.

	Slide
<i>The Bill & Melinda Gates Foundation</i>	2
Bill and Melinda Gates started the Foundation with the belief that every person should have the chance to live a healthy and productive life. This belief underlies all of the Foundation's work to reduce hunger, poverty, and disease around the world.	
The Foundation's headquarters are in Seattle. They also have offices in London (its Europe regional office) and Washington DC, as well as country offices in New Delhi and Beijing. Since 2012 they have had country representatives in South Africa, Nigeria and Ethiopia, representing their strong presence in Africa. Annual grants by the Foundation totalled US\$3.4 billion in 2012, with approximately \$600 million of that spent on research and development (R&D). In comparison, the pharmaceutical industry spends \$130 billion on R&D worldwide.	3
The Gates Foundation has three main Programs: Global Health, Global Development and the United States Program, the latter of which largely addresses education in the US. The Global Health Program addresses infectious diseases such as HIV, TB, malaria and polio, whereas Global Development focuses on agriculture, financial services, hygiene, neonatal child health and malnutrition.	4
<i>Focus of the Global Health Program:</i>	
<i>HIV</i>	6
The ultimate goal is to reduce the global incidence of HIV and to help people infected with HIV to lead long and productive lives. There is currently a focus	

on neutralising antibodies, whose success in non-human primates has created huge excitement. Human clinical trials are due to start shortly, so the efficacy of these drugs in human patients should become apparent by the end of the year. The main problem with the current anti-retroviral drugs is adherence to the treatment regimen, and there is huge concern about improving it.

Tuberculosis

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Tuberculosis (TB) mortality has fallen substantially in the past two decades, but TB remains a leading cause of death worldwide. The Gates Foundation's TB efforts include investing in developing and delivering better vaccines, treatments, and diagnostic tools. Its biggest efforts are in developing new drugs for treatment. There is an exciting new regime in its final stages of development which shortens drug treatment from six months to four months. It is hoped that this will improve adherence. In Dr Mundel's opinion, TB represents the most underfunded area in global infectious diseases; however, it remains a very difficult area to address.

Malaria

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The Gates Foundation aims to control, eliminate and ultimately eradicate malaria. There was an international call for complete malaria eradication in 2008, but no clear strategy for how to achieve this was outlined. Now there is a clear strategy for achieving the goal, which focuses not on the 5% who report to hospitals with malaria, but on the 95% who are asymptomatic carriers acting as a reservoir for the parasite.

Neglected Infectious Diseases

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More than one billion people in developing countries suffer from a multitude of infectious diseases that have historically attracted little donor funding. The neglected infectious disease agenda has recently shifted to an elimination objective. The disease African trypanosomiasis (sleeping sickness) is currently the closest to eradication. This is due to a combination of new point-of-care diagnostics, a new 10-day oral treatment introduced to replace a relatively ineffective intravenous treatment, and good vector control in the dense forests of central Africa. There is certainly the potential to eradicate this disease rather than simply control it.

Enteric and Diarrheal Diseases

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The Foundation works on a variety of interventions and treatments for gastrointestinal and diarrheal diseases, including vaccines for diseases such as rotavirus.

Pneumonia

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Pneumonia is the world's leading cause of death among children under five years of age. The Foundation is hoping to increase maternal immunisations with a combination of vaccines including pneumonia, RSV (Human respiratory syncytial virus), influenza and pertussis with the aim that this will ultimately make a big difference to neonatal survival.

Polio

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The world recently celebrated three years of polio absence in India, which is an unprecedented accomplishment that ten years ago would have seemed nearly impossible to many people. The current goal of the polio program is to eradicate the wild-type polio virus by the end of 2018. However, due to the extremely difficult geopolitical situations for delivering vaccinations in countries such as Nigeria and Pakistan, achieving this goal will not be easy or cheap to do.

Innovation in Global Health

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The Foundation is a key partner in the GAVI Alliance, which is saving children's lives and protecting people's health by increasing access to immunisation in poor countries. 50% of GAVI's vaccine suppliers are part of the 'Developing Countries Vaccine Manufacturers' (DCVMs) Network with the mission of increasing the quality and availability of vaccines affordable to all, and the Gates Foundation is very keen to invest in these. With GAVI support, an additional 370 million children have been vaccinated between 2001 and 2012, with a 36% drop in cost to immunise a child with pentavalent, pneumococcal and rotavirus vaccines.

In 2009, rotavirus vaccines were \$7.50 per dose, but due to an agreement with manufacturers GlaxoSmithKline, the price per dose dropped to \$2.50 by 2012. In 2015, rotavirus vaccines will drop to \$1 per dose. These shifts in economics have a huge impact on efforts to improve global health.

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Although the mortality rate of the under-fives in developing countries has halved since 1990, neonatal mortality rates have not declined on the same scale and now represent 40% of child deaths. There is clearly a residual problem that needs to be addressed; however, a key question is whether innovation or better delivery of existing simple solutions will solve this problem.

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Dr Mundel joined the Gates Foundation two and a half years ago, and came to understand that the technical hurdles for improving global health are higher in developing countries than they are in developed countries, mainly due to less effective or broken delivery systems. Simple solutions are often the most effective but in settings with broken delivery systems there might be a need to think of innovative solutions, including novel delivery systems.

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Creating innovative solutions for scientific challenges in the developing world poses a unique set of difficulties. Healthcare workers have encountered children with altered gut immune function and children who developed polio paralysis despite receiving 14 doses of the vaccine (in developed countries just two doses of the vaccine provides sufficient protection). The Gates Foundation is seeking to create solutions for patients with a weakened immune system, plus novel ways to boost vaccine responses, and combination vaccines to target multiple diseases in order to facilitate more efficient delivery and improve uptake.

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The fundamental R&D problem

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The current paradigm of research and development means that the end stages of drug development are hugely expensive; a single study might cost \$150 million at late stages when the risks for failure are still high. This is clearly not an ideal business model. The challenge now is to shift investment significantly to proof of concept stages, so that the risks can be understood at much earlier, cheaper stages. Therefore, when drugs under development do enter the very expensive Phase IIB/III trial stage there is a much better likelihood that the drugs will work as intended.

A good example of this principle is a company called Kymab which has developed the Kymouse – a mouse with a fully humanised B-cell antibody repertoire. This allows the development of human monoclonal antibodies and vaccine antigen discovery in a transgenic model. The use of this model will significantly improve the R&D cost/success ratio. It could be used to see if malaria, TB or HIV vaccines show the appropriate sustained responses, and provide early insights into further clinical development of vaccine candidates.

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Another example is one of the current strategies to test human malaria transmission. Healthy volunteers are vaccinated with a test article and exposed to mosquitoes infected with *P. falciparum*, then monitored and treated if necessary. This is a highly valuable model which yields huge benefits for malaria vaccine development. The Centre for Clinical Vaccinology and Tropical Medicine at the University of Oxford has one of the best uses of this model in the world. However, models of this nature require flexibility and may take a long time to produce results.

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Infrastructure limitations

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Developing countries can have inefficient supply chains. Medicines and vaccines need to be kept cool, and the large packages in which they are shipped in are designed for developed countries, not small health centres in rural developing countries. Healthcare workers do not always provide sufficient notice when stocks are low and consequently regularly run out of products. It is the worst case scenario that a mother travels a long way to reach a clinic, only to find that there are no doses left with which to vaccinate her child. Unfortunately, these issues occur regularly.

An NGO called Village Reach in Mozambique came up with an excellent, simple solution to this issue. Instead of waiting for orders, Village Reach distributes the drugs directly to the health centres proactively. Trucks visit villages with their full inventories kept cool in the back, and healthcare workers select what they need. Implementing this system led to a reduction in the incidence of vaccine stock shortages in rural health centers from 80% to 1%, as well as an increase in the percentage of children receiving basic vaccines from 69% to 95%. Margarida Matsinhe, the founder of Village Reach, won the Gates Vaccine Innovation Award for her efforts. She is particularly rigorous, and the successes of campaigns like these are always dependant on local champions like Margarida.

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Access and affordability

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An effective and appropriate global health solution must also be made available at an affordable price point. However, the pharmaceutical and biotechnology industries are not necessarily attracted to markets in developing countries. The Gates Foundation provides financial support to industry to lessen the risk of investments in global health products. It also makes equity investments in start-up companies that can be particularly helpful for developing promising solutions for global health.

Dr Mundel noted that the UK has been central to GAVI Alliance funding. The UK is one of GAVI's six original donors and one of two donor countries that support GAVI through all three of its funding channels. The UK had contributed approximately \$2.3 billion to GAVI in total as of December 2013. For the period of 2000 to 2030, the UK has pledged over \$5 billion more in support to GAVI. Pentavalent vaccine distribution has now commenced in all GAVI-supported countries except South Sudan; however successful vaccine administration to the public is lower, with the coverage in these countries currently at approximately 43%.

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Importance of data analytics and measurements

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It is impossible for global health to improve if we don't know the exact situation of the world now. Therefore data are the fundamental tools on which efforts can be developed, and the Gates Foundation has invested heavily in data analytics and measurements.

As an example, the Malaria Atlas project has been hugely informative and has allowed detailed micro-planning towards malaria control and elimination. The aim of this work was to develop open-source global maps of epidemics to estimate populations at risk. These spatial data are very important, as the malaria campaign demonstrated, with many hamlets and villages that weren't previously on government lists for distribution now targeted with vaccines and therapies.

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As well as examining localised distributions of diseases, understanding the global burden of disease (GBD) is also of critical importance. The 2010 report on GBD¹ was the first standardised, comprehensive platform to quantify global health data by geography, age, and sex. The GBD 2013 report is due to be published soon. The goal is to inform decision-making and maximise health system impact; however there is still a fundamental issue with primary data quality. Ideally accurate, real-time primary data from the whole world would be used, but data from developing countries are often poor. Developed countries like the UK can really benefit from the huge analytical studies that the Gates Foundation funds, as the data from the UK are of high quality. It will allow analysis at a sub-national level, and provides insights into the areas that

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¹ Murray CJL *et al.* (2012). Global Burden of Disease Study 2010, *The Lancet*, Vol. 380: 2053-2260

the UK is lagging behind other developed countries². For instance, it can provide data on mortality or disability-adjusted life years (DALYs), and can disaggregate these into information on a large number of diseases and countries.

The Gates Foundation does not have a focus on non-communicable diseases despite the rapid global increase in these, which includes developing countries. Although the proportional burden of communicable diseases has significantly reduced since 1990 in Latin American and Caribbean countries, it is not the case in Sub-Saharan Africa. In these countries the burden heavily remains on communicable diseases, and so the Gates Foundation remains committed to targeting communicable diseases at this time.

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Guiding investments in global health

The Gates Foundation has to ensure cost effectiveness in its investments. It does this by calculating the dollars per DALY averted and the chance of averting it, i.e. the amount it costs to avert one year of disability-free-life per person versus the probability of success. For example, data shows that surgical male circumcision represents a very cost-effective intervention to promote, because it is so effective in reducing the spread of HIV. Similarly, bed nets are a highly cost-effective method to help prevent malarial infection.

More recently, this principle has guided the Foundation's announcement that \$122 million is to be spent in new commitments toward three soil-transmitted diseases that affect nearly one in four people worldwide - hookworm, roundworm, and whipworm. This includes \$50 million from the Children's Investment Fund Foundation (CIFF) to support school-based treatment programmes for soil-transmitted helminth (STH), where they are hoping for 75% coverage.

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They can also use analysis to prioritise certain projects. For example, the hookworm vaccine was calculated to cost \$10,000 per DALY, yet had only a medium probability of success. Compared to investing in the mass drug administration (MDA) initiative to treat hookworm, the hookworm vaccine was not very cost-effective, and is now considered a low priority.

Partnerships and Collaborations

The Gates Foundation would make no progress at all without their partnerships, including significant collaborations with UK-based partners, which are very important to them.

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The London Declaration describes a coalition of partners from the public and private sector that came together in 2012 and committed to controlling or eliminating 10 neglected tropical diseases by 2020. The pharmaceutical industry is donating the medicines needed to accomplish these goals. These partners then support the development of national plans by endemic countries

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² Murray CJL *et al.* (2013). UK health performance: findings of the Global Burden of Disease Study 2010, *The Lancet*, Vol. 381: 997–1020

to outline how they will map disease distributions, deliver treatment, and monitor progress towards control and elimination. Last year was the first year that drug supply was not an issue for achieving these goals; however, the eventual delivery to patients in all areas remains a considerable hurdle.

Grand Challenges Grants

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The Gates Foundation supports grants for Grand Challenges Explorations, Grand Challenges in Global Health and in-country partnerships. 'Grand Challenges Explorations' is a biannual \$100,000 grant programme which involves a two-page application with a novel idea. These have been awarded to a broad range of people that represent new types of innovation, with young people being highly successful applicants. These differ from the larger Grand Challenges in Global Health grants which are more structured proposals to tackle specific problems. In-country partnerships include the USAID's Grand Challenges for Development program; programmes run by the organisation Grand Challenges Canada; and programmes run through the Grand Challenges India, Brazil, and Israel partnership frameworks. A number of these countries are now matching the funding given to them by the Gates Foundation, doubling the grant-holders' budgets. To date, they have completed eleven rounds of proposals, yielding over 40,000 applications from 182 countries. Today, more than 900 Grand Challenges Explorations grants have already been awarded for innovative, early-stage projects in more than 50 countries.

Past topics for the Grand Challenges Explorations grants include developing the next generation of condoms, creating low-cost mobile phone based applications for priority global health conditions, and the 'reinvent the toilet' challenge, which had its second global fair in Delhi recently. A recent project involves exploring new ways to measure fetal and infant brain development, which will hopefully allow researchers to understand the impacts of environmental and nutrition factors on brain development.

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Gates fellows and interns

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The Gates Foundation has just started its Fellows programme, which are two-to four-year positions designed to develop Fellows' capabilities, skills and understanding of the Foundation. The Fellows in turn provide access to fresh talent and perspectives to advance the Foundation's way of thinking, and contribute in a substantive way to the global health field.

Discussion

The lecture was followed by a discussion, which is summarised below.

The Post-2015 Millennium Development Goals (MDGs)

Dr Mundel acknowledged the importance of considering global health work alongside the post 2015 MDGs. For the Foundation this might include considering how much it should continue to invest in its ongoing goals, and when resources should be reallocated to address something new. He emphasised that the Foundation is committed to looking at

all aspects which have an impact on global health by continuing to work towards previously held objectives, but remaining serious about upcoming challenges. Many of these are unavoidable inclusions to address as part of existing goals; for example, climate change will impact on dengue fever and malaria distributions, due to temperature and flooding changes.

Understanding the uncertain causes of poor treatment adherence

The example of HIV treatment was used to highlight the many causes of, and potential solutions to, poor adherence to drug regimes, such as a lack of understanding by patients, complicated regimes, non-users on matters of principle, and political opposition.

Dr Mundel said that this is certainly an issue for his Program, and that the HIV campaign has always been affected by local or cultural attitudes, with certain countries maintaining HIV denial for a long time. However, even countries or regions with a good education system, good infrastructure and a low prevalence of HIV - such as in the Western Cape - still see significant non-compliance with therapies, which highlights the complicated nature of drug adherence. Even the US observes significant non-compliance for blood pressure drugs for example. Nonetheless, there are improvements: historically, the average HIV patient turned up at the clinic with a CD4 cell count at less than 50. The average CD4 count of new patients is now over 200, suggesting that more people are coming to clinics earlier in response to campaigns to increase awareness about seeking treatment.

The hurdles for implementing innovation

In response to a contribution about investment in health science and implementation research to reduce the hurdles for introducing innovative developments, Dr Mundel noted that the Foundation has a real interest in operational research, which is deemed important in implementing innovation. He also noted that there is sometimes the impression that the Gates Foundation is not interested in funding brick and mortar projects. This is because those sorts of projects are massive enterprises, and the Foundation is not focussed on building hospitals and other healthcare infrastructure. Governments have the responsibility to invest in basic infrastructure, and the Foundation can assist with many aspects on top of this, including IT, logistics and delivery, which aid the implementation of innovation.

The importance of water access and sanitation

Dr Mundel outlined that the Gates Foundation has a substantial interest in water access and sanitation, although it is not one of their biggest programmes. He supported the notion that solving some of these issues could represent lasting solutions and that there is clearly the need to cover ground on these areas: for example, the burden of typhoid in Africa is not known, despite the continent's health being a primary focus of the Foundation. The integration of a lot of issues will be essential for the development of post-2015 MDGs, building from the original MDGs to eradicate poverty, which included access to clean water.

The digitisation of health information

In response to a question about embracing digitisation to aid more tailored solutions, Dr Mundel noted that considering Bill Gates's background, many might assume that the Foundation would be at the forefront of digitising everything. However, he warned that careful scrutiny is required to avoid false claims of digitisation benefits. Technology can have negative effects if rushed out prematurely: for example, some clinics work fine with a pen and paper, and don't want or need the added complication of a smart phone app. In India, there has been a very successful step into telemedicine; new software was implemented alongside teams of programmers in local clinics to make alterations as required. This was far more effective than someone in Seattle or London developing a blanket technology and shipping it straight out for application in clinics in Ghana and elsewhere universally.

Engaging of pharmaceutical companies in global health

Dr Mundel highlighted the London Declaration on neglected tropical diseases as a good example of engagement with the pharmaceutical industry working very well. Previously, pharmaceutical companies were not integrated into programmes properly, but now they have a very significant role and this is likely to reinforce the importance of continued investment.

The role of improved technology alongside low government infrastructure investment

Dr Mundel suggested that MDA campaigns can be delivered in many different ways, in response to a question about the balance between filling gaps on infrastructure investment, where governments fail to do so, and focusing on technological and innovative solutions to delivering care. Dr Mundel said that the ideal method is to have government involved, but that this is not always essential. There is a significant lack of government control in places like northern Nigeria, Pakistan and the Democratic Republic of Congo, but the Foundation has still managed to deliver polio vaccines in these regions. NGOs are another extremely useful way to deliver MDAs; for example, delivery in Haiti is now quite good, facilitated by local NGOs.

The increasing importance of non-communicable diseases (NCDs) in developing countries

Dr Mundel reiterated that the Gates Foundation is focussed on communicable diseases at present, but would always like to hear about other issues. He stated that if these problems increase further in the world's 70 poorest countries then the Foundation would certainly rethink its position. It is a daily challenge to make decisions on what to fund; the Gates Foundation needs to have some focus and discipline, but always want to allow for new ideas to be considered. The Foundation's campaigns towards sleeping sickness eradication had a real opportunity to make a huge impact, whereas an equivalent investment in reducing NCDs in the target countries may not have had as much impact. Obviously, the Foundation's campaigns have to depend on cost-effectiveness to determine funding choices.