

Recent Trends in Global Immunisation

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1 Introduction

In the midst of the global financial crisis, it may be difficult to argue that increased aid to the poorest countries, particularly those in Africa, is of high priority. Nevertheless, a dissection of recent trends in global immunisation should be embedded in an analysis of the global health scene. It could be argued that some global inequities are just intolerable and that therefore inertia and indifference are no longer possible. That being said, it is encouraging that global immunisation programmes are on the improve and that despite everything progress in global health is possible.

2 Official Development Assistance at the Global Level

After the Gleneagles meeting of the group of eight richest nations in 2005, a decision was taken to increase aid substantially, particularly to Africa. In the event, while not every country has lived up to its pledges, total Official Development Assistance in 2008 rose by 10.2% from the 2007 base, reaching US \$119.8 billion or 0.3% of global Gross National Income. Of that, aid to sub-Saharan Africa was US \$22.5 billion. Bearing in mind that the United Nations many years ago set 0.7% of Gross National Income as the desirable benchmark, it is interesting to note that only five countries actually managed to reach that goal, namely Denmark, Luxemburg, The Netherlands, Norway and Sweden. In terms of actual monies contributed, the volume leaders are USA (\$26 billion but only 0.18% of Gross National Income), Germany, UK, France and Japan in that order. Following a strong commitment by the Rudd Government, Australia's aid rose 13.8% in 2008 to 0.33% of Gross National Income. It is planned to go to 0.5% of GNI by 2015.

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One frequently hears an argument against overseas aid which suggests that aid is not worthwhile because of rampant corruption and what is really needed is increased trade with developing countries. Actually, saying that aid is all wasted on corruption is a bad excuse for doing nothing. It is true that there is much corruption in developing countries, and it is important to “corruption proof” particular grants as much as possible, but for the poorest countries frankly there may be nothing to trade without aid. Unquestionably, reduction of trade barriers would be very helpful to developing countries and therefore the real answer is that we clearly need both trade and aid. It is essential to realise that aid works only if there is a true partnership, and the methods of giving aid need careful examination. For example, micro-credit has a proud history in the short time that it has been promoted.

An important point to make is that the world, even in a global financial crisis, can increase aid if it truly wants to. Indeed, the global financial crisis shows just what huge funds governments can mobilise if the will is there. For example, the US Wall Street Bailout cost US \$700 billion and the G20 stimulus packages agreed at the recent G20 Summit meeting totalled well over US \$1 trillion. The wars in Iraq and Afghanistan cost the USA alone US \$150 billion/year. Putting this into perspective, it has been estimated that most of the Millennium Development Goals could be achieved if an extra US \$120 billion/year in Official Development Assistance were available, i.e. a doubling of the present level and still short of the 0.7% GNI benchmark.

Increasing aid does not depend upon the decisions and pronouncements of politicians alone. It becomes feasible when ordinary people become committed realising that it is in the long-term interest of social stability and peace. The matter is well summarised by the following two quotes:

Each of the great social achievements of recent decades has come about not because of government proclamations, but because people organised, made demands, and made it good politics for governments to respond. It is the political will of the people that makes and sustains the political will of governments. (The late James Grant, former Executive Director of UNICEF)

Every day, 50,000 people die needlessly as a result of extreme poverty. Poverty can be eradicated only if governments of both developed and developing countries live up to their promises. (Ban Ki-moon, Secretary General UN, 2008)

3 Health Progress is Possible

Nothing illustrates more starkly the degree of global inequities in health than life expectancy and mortality statistics. Some illustrative examples for 2007 are given in Table 1. How can we continue to live in a world where life expectancy is twice as long in the “best” countries than in the “worst”, let alone where deaths under 5/1,000 live births are nearly 100-fold different between “best” and “worst”?

Despite these alarming statistics, it is clear that health progress is possible. For example, when we look at the under 5 mortality, this was a record low of 9.2 million deaths in 2007 vs. 13 million in 1990 despite an increased population. It comes as no

Table 1 Life expectancy and mortality statistics 2007

	Males	Females
	<i>Life expectancy</i>	
Japan	81	86
Australia	79	84
USA	76	81
Afghanistan	41	42
Sierra Leone	39	43
	<i>Deaths under 5 per 1,000 live births</i>	
Sierra Leone	262	
Afghanistan	257	
USA	8	
Australia	6	
Japan	4	
Sweden	3	

surprise that the bulk of these deaths were in sub-Saharan Africa (4.5 million) and in South Asia (3.0 million). About two-thirds of these deaths were preventable, among these were pneumonia (1.8 million), diarrhoea (1.6 million), malaria (780,000), measles (390,000) and AIDS (290,000).

In part, this health progress has been secured through some massive new programmes since the year 2000, of which the largest are the Global Fund to Fight AIDS, TB and Malaria initiated in 2002; the President's Emergency Plan for AIDS Relief (PEPFAR) initiated in 2004; and the many programmes of the Bill and Melinda Gates Foundation starting from the year 2000. These new and very large programmes should not obscure the fact that other and more traditional programmes are getting traction, including polio eradication, the Stop TB Partnership, various malaria control programmes, and ambitious plans to contain filarial diseases including river blindness and lymphatic filariasis.

4 The GAVI Alliance, Formerly the Global Alliance for Vaccines and Immunisation

A major example of a Gates Foundation-initiated programme is the GAVI Alliance [1]. Launched in 2000, this has three main aims, namely increased coverage in the poorer countries with the standard childhood vaccines; introduction into immunisation programmes of newer vaccines; and increased research and development of new and improved vaccines for third world use.

As a result in its relatively short history the GAVI Alliance has ensured that a cumulative 51 million extra children got their three doses of the diphtheria–pertussis–tetanus vaccine, a surrogate for the six common childhood vaccines. A

cumulative 192 million children have been immunised with hepatitis B, and coverage with this important vaccine is now 60% worldwide. A cumulative 42 million children have been immunised against *Haemophilus influenzae B*, and given that this conjugate vaccine was so successful, the Gates Foundation has helped to introduce conjugate pneumococcal vaccines as well. Planning is well advanced for introduction of rotavirus vaccines and vaccines against typhoid, rubella, Japanese encephalitis and cervical cancer.

As a result of the above initiatives, it is estimated that a cumulative number of 3.4 million deaths have been averted.

One fine example of what can be achieved with developmental research and technology transfer is the plan to control the shocking outbreaks of meningococcal meningitis that sweeps across the so-called meningitis belt of sub-Saharan Africa. In a partnership between the Gates Foundation, the World Health Organization (WHO) and the non-governmental organisation PATH (Program for Appropriate Technology in Health), the Serum Institute of India was contracted to develop a meningitis A conjugate vaccine and helped with significant technology transfer. They have pledged to make the vaccine available at US 40¢ per dose. They have already succeeded in showing that the vaccine is 20 times more immunogenic in 12- to 23-month-old children than the carbohydrate vaccine, through trials in Mali, The Gambia and in Ghana. The Dell Foundation has pledged to fund a demonstration study in which all 1- to 29-year-olds in Burkina Faso will be given a single dose of the vaccine in 2009–2010. In parallel further large phase III trials in Mali and India are planned for 2009–2010. If successful, and there is little reason to doubt that the trials will be successful, 250 million 1- to 29-year-olds and 23 million infants in 24 other “meningitis belt” countries will be immunised between 2010 and 2015. The result would be to protect 430 million people in 25 countries from Senegal to Ethiopia from this horrible disease with its 10% case fatality rate and 20% of serious sequelae, including mental retardation.

5 Polio Eradication Still Somewhat Problematic

Within the field of immunisation some areas are still problematic. For example, the polio eradication campaign is way behind where its planners hoped it would be at this stage. There are still four countries (Nigeria, India, Pakistan and Afghanistan) in which transmission has never been interrupted. Furthermore, 14 countries in which poliomyelitis had been eradicated have reported re-introduction, admittedly small numbers of cases, but showing that the threat is still quite real.

Dr. Margaret Chan, the Director-General of WHO, has termed polio eradication as WHO’s top operational priority. With respect to the fact that it is proving so difficult to immunise children in some of the poorest areas, such as Northern India, the question has been raised as to whether the injectable polio (Salk) vaccine may need to be used in such areas. Furthermore, given the occurrence of intercurrent diarrhoea, it has been postulated that zinc supplementation may have a role to play.

6 Recent Developments in Malaria

There has recently been considerable public health progress in the field of malaria [2]. Of course malaria remains a very serious public health problem. There are at least 300 million attacks per year, at least 1 million deaths, mainly in children under 5, and resistance of the parasite to first-line, cheap drugs and also resistance of mosquitoes to insecticides remain big problems. However, progress has been on three fronts. Insecticide-impregnated bednets pre-sprayed with pyrethroids have proven a singularly effective and relatively cheap weapon. At less than \$5 per bednet, malaria mortality has been decreased by more than 50%, resulting in the fact that all-cause mortality has been reduced by 20%. This has been a real boon in areas of high malaria endemicity. Frequently it has been accompanied by residual spraying of dwellings by pyrethroids as well. Second, after a rather fallow period, new drugs for malaria are at last coming forward. For example, the “Medicines for Malaria” venture represents a public–private partnership between the WHO and 39 research and development partners. Initiated in 1999 it already has 11 drugs in clinical trials. Many of these are derivatives of artemisinin. In fact, artemisinin-based combination therapy (ACT) is now best practice for attacks of malaria. Some combinations include chlorproguanil–dapson–artesunate, pyronaridine artesunate and also artemisinin together with drugs like amodiaquine or piperaquine. A related step forward is intermittent preventive treatment (IPT) for malaria in infants. This involves a full course (for example of sulfadoxine–pyrimethamine) given to asymptomatic infants in areas of high risk. Similarly, IPT is also effective in pregnancy, frequently with two courses given during the pregnancy. Third, there has been progress on the malaria vaccine front. A vaccine prepared by GlaxoSmithKline called RTS,S based on the circumsporozoite protein showed a 66% efficacy in 554 African infants when given as three doses at 10, 14 and 18 weeks of age. In view of these encouraging results, phase 3 trials have been started in nine countries and should finish by October 2011. It is planned to enrol 16,000 infants aged 5–17 months in ten different sites in seven countries.

RTS,S is not the only progress in malaria vaccines. For example, the Gates Foundation is backing a whole portfolio of alternative approaches. The firm Sanaria is embarking on clinical trials of live X-irradiated mosquito salivary gland-derived sporozoites following trials in human volunteer challenge studies that showed 90% efficacy. A wide variety of blood stage antigens are in late pre-clinical or early clinical development. Liver cell-specific antigens are being progressed, particularly by the International Centre for Genetic Engineering and Biotechnology in New Delhi, India. Various vaccines depending on viral vectors, leading to T-cell immunity, are under development, frequently with protocols favouring a “prime–boost” approach, i.e. a different vaccine for the priming and the boosting protocol.

In view of all this activity, in September 2008 the United Nations called a special summit meeting and launched a \$3 billion plan to “end all malaria deaths by 2015”. While this might be unduly optimistic, it is an indication of how seriously the malaria control field is moving.

7 HIV/AIDS Vaccine – A Long Way to Go

The news is not as good with respect to an HIV/AIDS vaccine [3]. The failure of Merck's adenovirus 5-vectored vaccine efficacy trial in 2007 was a big disappointment. At the time of writing, the Sanofi-Pasteur ALVAC-HIV prime VaxGen gp120 boost vaccine in adult Thai men is the only efficacy trial ongoing. Other T-cell-based strategies include novel vectors (non-human adenoviruses, CMV, NDV, measles, fowlpox, BCG) sometimes encoding interleukins, dendritic cell targeting ligands or TLR ligands. These strategies usually involve prime–boost protocols.

Antibody-based strategies for an HIV/AIDS vaccine fall into two groups. First there are attempts to define the epitopes which bind broadly neutralising monoclonal antibodies, which are then synthesised or mimotopes of them constructed. Then there are attempts to target the conserved, briefly revealed co-receptor binding site on the envelope protein. These could be conformationally constrained gp120-CD4 constructs, computer-generated mimotopes or peptide-scaffold molecules.

One problem which constrains all HIV/AIDS vaccine research is the lengthy and difficult process of clinical trials, particularly given that ethical concerns mandate that strict safe sex education must be given at all trial sites, with documented evidence that this alone reduces rates of acquisition of seropositivity.

8 Measles Remains a Threat

With all this activity in research on vaccines which do not yet exist, it is easy to forget that in the developing countries measles still remains a real threat. For reasons that are not entirely clear, the case fatality rate of measles in a developing country setting is up to 2%, very high for a disease which essentially every non-vaccinated child gets at some time. A serious problem with respect to measles vaccination is that the live attenuated vaccine can usually not be given before 9 months of age. As maternal immunity wanes at about 4 months of age, there is a substantial gap during which infants remain highly vulnerable.

This induced a group led by Dr. Peter Aaby in Guinea-Bissau [4] to go against the conventional wisdom and to trial measles immunisation at 4.5 months of age. A group of 441 children in Guinea-Bissau received such immunisation vs. 892 children that remained in the control group before both groups were given the regular 9-month dose of the live attenuated measles vaccine. Monthly measles incidence was charted and turned out to be 0.7% in the immunised group vs. 3.1% in the control group. Cumulatively, by 9 months of age, 14.4% of unvaccinated but only 3.1% of vaccinated infants had contracted measles. Even more startling was vaccine efficacy against admission to hospital for measles, which was 100%. Equally, deaths from measles were 7 in the unvaccinated but 0 in the vaccinated, again 100% efficacy. The treatment group had no more non-measles deaths than controls.

It is clear that this was a relatively small and preliminary trial. Nevertheless the results are sufficiently intriguing as to warrant serious follow-up.

9 Anti-Vaccine Activists are a Real Danger

Unfortunately, anti-vaccine activists constitute a real danger in both the industrialised and the developing countries. In the richer countries, these activists are emboldened by the fact that most mothers have little or no experience of how fierce epidemic disease can be. Two recent examples illustrate the point. In the United Kingdom, claims that the measles–mumps–rubella vaccine caused autism saw a disastrous drop in immunisation coverage, at a time when measles transmission had practically come under control. This necessitated extensive and expensive studies to disprove the claim but the UK immunisation programme has still not fully recovered. In France, false claims that the hepatitis B vaccine could cause multiple sclerosis seriously set back the use of this important tool.

The worst example in a developing country comes from Kano State in Nigeria. Here, a rumour spread that the oral polio vaccine was really a Western plot to render female Muslim babies sterile. This entirely fanciful notion caught hold, derailed the polio eradication effort for more than a year and resulted in the fact that polio became resurgent in Nigeria and, just as disastrously, polio spread from Nigeria to numerous neighbouring African countries. Through belated government action, the polio immunisation programme in Nigeria is now more or less back on track, but harm such as this takes a long time to undo.

The fact of the matter is that serious adverse events after immunisation do occur, but are vanishingly rare. For example, the oral Sabin polio vaccine can occasionally revert to neurovirulence, but this occurs approximately once per 2 million doses! The measles vaccine can very rarely cause thrombocytopenic purpura, but at an incidence that is at least 1,000-fold less than that at which measles itself causes this complication. Other claims, such as encephalitis after the pertussis vaccine, have also not been proven. The risk–benefit equation is enormously on the side of vaccine benefit.

10 Conclusion

There is room for cautious optimism in the global public health scene. It is clear that the Gates Foundation has unleashed some powerful and dynamic forces. Equally, it is evident that some governments are taking their responsibilities towards developing countries more seriously. The emergence of talented and idealistic health leaders in many developing countries is also to be welcomed. The statistics are there for everyone to see and it will take some time for them to become less scandalous. What is needed is the continuance of scientific progress and political will.

This chapter has been as much about politics as it has been about science. As it is based on a lecture given at Oxford University, it may be apt to end with a quote from one of Oxford's greatest sons. Sir Peter Medawar said: "If politics is the art of the possible, research is surely the art of the soluble. Both are immensely practical-minded affairs".

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