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Hot Topics in Infection and Immunity in Children VII

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Preface

Each of the chapters in this book is based on a lecture given at the seventh 'Infection and Immunity in Children' (IIC) course held at the end of June 2009 at Keble College, Oxford. Thus, it is the seventh book in a series, which collectively provide succinct and readable updates on just about every aspect of the discipline of Paediatric Infectious Diseases.

The eighth course (28–30 June 2010) has another exciting programme delivered by renowned top-class speakers, and an eighth edition of this book will duly follow.

The clinical discipline of Paediatric Infectious Diseases continues to grow and flourish in Europe. The University of Oxford Diploma Course in Paediatric Infectious Diseases, started in 2008, is now well established with a large number of trainees enrolled from all parts of Europe. The Oxford IIC course, as well as other European Society for Paediatric Infectious Diseases (ESPID)-sponsored educational activities, is an integral part of this course.

We hope this book will provide a further useful contribution to the materials available to trainees and practitioners in this important and rapidly developing field.

Melbourne, Australia — Nigel Curtis
Bristol, UK — Adam Finn
Oxford, UK — Andrew J. Pollard

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Sue Sheaf has administered and run the course for several years now. Her quiet efficiency and effectiveness are vital to its success. As course organisers we are indebted to Sue and we are enormously appreciative of her efforts. We give our heartfelt thanks to Sue on our behalf and also on behalf of all the speakers and delegates who have benefited from her behind the scenes administrative, organisational and diplomatic skills.

Pamela Morison administered the production of this book. In addition to carefully correcting and formatting the chapters and liaising with the publishers, she quickly learnt the subtle art of persuading authors (and editors) to meet deadlines, read formatting instructions and answer e-mails. We thank Pam for her patient and cheerful approach to this difficult task, and we gratefully share with her the credit for this book's production.

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Finally, we are grateful to several pharmaceutical industry sponsors who generously offered unrestricted educational grants towards the budget for the meeting.

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Speakers at the Infection and Immunity in Children 2009 meeting in Keble College, Oxford University

The Value of Vaccination

David E. Bloom

Abstract Vaccination is most often studied from a scientific, clinical, or epidemiological perspective, and rightly so, for vaccines are meant to improve health outcomes. But these are not the only lenses through which the effects of vaccination programs can be understood. This chapter provides an economic perspective on vaccination programs, detailing in particular a new line of inquiry that makes a case for the importance of vaccination to achieving national economic aims. Research has shown that national spending on childhood vaccination programs does more than just reduce morbidity and mortality in a country: it also promotes national economic growth and poverty reduction. The chapter begins with a look at recent research that demonstrates powerful links that run from population health to economic well-being. Second, it discusses how knowledge of the economic benefits of health fundamentally transforms how we understand the value of vaccination. And third, it provides evidence for the scale of the returns that countries receive when they invest in immunization programs – returns that have not been fully captured by traditional economic analyses.

1 Population Health and Economic Well-Being

Since 1950, many parts of the world have seen remarkable health gains. Life expectancy has increased by more than two decades, and the global infant mortality rate has been reduced by two-thirds over the same time period. Smallpox has been eradicated, and polio nearly so. These health improvements are examples of what one might consider truly extraordinary achievements. By defining what might be possible, they can – and should – make us even more ambitious about what can be achieved in the future.

But these have also been accompanied by a colossal set of failures in the health arena, failures that indicate the extent and severity of human misery and insecurity

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on the planet. In particular, there has been a demonstrated reversal of health gains in some countries. Largely as a consequence of the HIV and AIDS epidemics, life expectancy in several sub-Saharan African countries has fallen, in some cases by roughly 15 years, beginning in the 1990s [1]. As another example, two-thirds of the roughly 9 million deaths of children under the age of 5 worldwide that will occur this year will be due to causes that could be easily prevented or cured with existing knowledge [2].

Even more troubling than these health deficits are the gross health disparities between rich and poor nations. In 2005, 86% of the world's health expenditure took place in the OECD countries – which are home to but 15% of the world's population [3]. At least 20% of the world's children are still not immunized with DTP3, with research in *The Lancet* suggesting that this number is likely to be closer to 26% [4]. Child mortality is currently an order of magnitude higher in developing countries than it is in the wealthy industrial countries. Significant disparities also prevail in infant mortality and life expectancy (see Table 1). Large disparities also exist not only between but also within countries, typically between urban and rural populations, racial and ethnic groups, and income classes.

Most of the financial resources for improving population health – for addressing these failures and disparities – will have to come from the public sector. There are four classic arguments in support of devoting public resources to the promotion and protection of health. The first set of arguments has moral, ethical, and humanitarian roots – i.e., devoting resources to health is fair and just. The second argument is that health is a "fundamental human right," a legal claim to which all human beings are entitled. The third argument is that health is essential to building strong societies. In this view, improved health is a key ingredient in the formation of social capital and societies that are cohesive, peaceful, equitable, and secure. A fourth argument has to do with the character of health and of health services, from an economic standpoint. For a number of reasons, unregulated markets do a poor job of achieving socially

Table 1 Health disparities between developed and developing countries [5]

	1950–1955			2005–2010		
	World	Developed countries	Developing countries	World	Developed countries	Developing countries
Infant mortality rate (deaths per 1,000 live births)	152	59	174	47	6	52
Child mortality rate[a] (deaths per 1,000 live births)	109	18	122	71	8	78
Life expectancy (years)	47	66	41	68	77	66

[a]Child mortality rate is for 1980–1985 and 2005–2010

desirable levels of health provision. This means that governments have a natural (and essential) role to play in the health sector.

These four arguments on behalf of devoting public resources to health are each logical and coherent. However, neither individually nor collectively have governments or other institutions been able to use them to mobilize the resources necessary to make a significant dent in the world's health deficits and disparities. It is evident that more is needed to make a persuasive case.

Another powerful justification for devoting public resources to health has recently come to the fore, one that will perhaps add to the collective power of the above justifications for health spending. This argument has to do with the relationship between health and the macroeconomy. Essentially, it argues that a healthy population is an important engine of economic growth [6].

Figure 1 shows one of the best established patterns in the field of global health – the positive association between health and wealth. Each point is a country, with the location of the point reflecting the country's income per capita and the life expectancy of its people. The basic pattern shown on the chart is that countries with higher incomes tend to have healthier populations. This pattern holds for different income and health measures and at different points in time [7].

Another key feature of the chart is the arrangement of the variables on the horizontal and vertical axes. Income is placed on the horizontal or *X* axis, which means it is the independent variable. This is a clear suggestion that the variable income affects the dependent variable on the vertical or *Y* axis, in this case, health. In other words, the centerpiece of this very famous scatterplot is a causal link that runs from income to health.

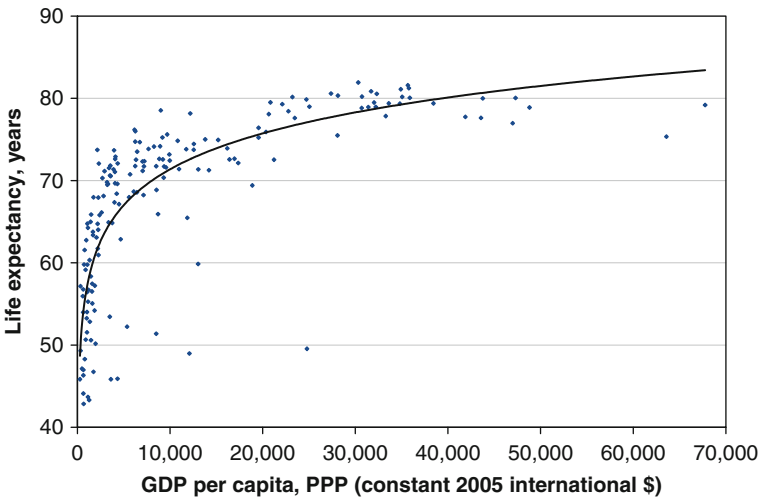

Fig. 1 Life expectancy and income [8]

This is not a startling idea. When people have more money, they tend to have better nutrition, better access to safe water and sanitation, access to more and better health care, and better psychosocial resources like community recreation facilities. These mechanisms allow one to conceptualize population health as a consequence of economic growth, which has been the dominant view on the health–income nexus going back to the birth of modern economics over two centuries ago.

However, the reverse causal link – from health to income – may be equally plausible, for several reasons [9]:

First, a healthier workforce tends to be a more productive workforce, with more energy, better mental health, and less absenteeism.

Second, economic outcomes can be improved through better education, which is in turn improved by health. Healthy children tend to stay in school longer and have better cognitive development. Thus, educational investments in healthy children yield high returns, which will naturally lead to an expansion of those investments. Education is virtually undisputed among economists as being one of the most powerful instruments of economic growth and poverty alleviation.

Third, health and longevity affect savings and investment. Healthy populations have higher savings rates as people save more in anticipation of longer periods of retirement. Savings lead to investment, which results in the accumulation of physical and human capital, and technological progress. These are, of course, the classic drivers of economic growth. It is also worth noting that healthy populations are better able to attract foreign direct investment [10], which often carries with it new technology, job creation, and increased trade.

Finally, demographic change provides yet another casual link from health to economic improvement, a link that was vitally important to the so-called economic miracles experienced in a number of countries in East Asia and Ireland. Essentially, the idea is that health improvements trigger a process of demographic change, beginning with lower fertility rates, that promotes an age distribution that is increasingly favorable to economic growth. This demographically induced boost to economic growth has come to be known as the demographic dividend.

The reverse link from health to income has been the subject of much statistical and econometric analysis in the past few years. There are different ways of looking at the link and at data pertaining to the link – varying time periods, control variables, data sets, statistical tools, theoretical frameworks, etc. For the purposes of this chapter, it is enough to say simply that population health is an exceedingly robust and powerful predictor of economic growth.

This premise can be illustrated through a thought experiment: Imagine two countries that are identical in all key dimensions pertinent to economic growth, except that the people in one are healthier than those in the other. The new finding tells us that the healthier country will increase its average income and reduce its poverty rate faster than the less healthy country. It also tells us that a 5-year advantage in life expectancy translates into between 0.3 and 0.5 additional percentage points of annual growth of income per capita [11].

A 1% point advantage may not sound like much, but in a world economy in which per capita income typically grows at 2–3% per year, it is quite meaningful.

A 1% point gain is also meaningful because a 10-year gain in life expectancy is well within the grasp of a very large number of countries. It corresponds roughly to the life expectancy improvement that developing countries – where average life expectancy is currently 66 years – would enjoy if they achieved the same life expectancy as today's developed countries – where it is currently 77 years. It also corresponds to the life expectancy improvement that many demographers project for the wealthy industrial countries during this century.

2 A New Paradigm for the Value of Vaccination

The new perspective outlined above has important implications for assessing the value of immunization programs. There are two standard approaches to conducting an economic evaluation of the desirability of a health intervention: cost-effectiveness analysis and benefit–cost analysis. Today, benefit–cost analysis is the economic tool of choice with respect to assessing the value of vaccination [12].

In carrying out a benefit–cost analysis, decisions must be made regarding what constitutes a cost and what constitutes a benefit. With respect to vaccination, there is nothing particularly tricky about measuring costs. These include the cost of the immunizing agent, the cost of administering that agent, and the value of time associated with getting a child to a medical practitioner, along with any associated transportation costs.

The calculation of benefits is less straightforward. Economists traditionally focus on a narrow range of implications of vaccination programs. They assume that with vaccinated children not getting sick, medical costs are avoided. In addition, they assume that parents may benefit by not having to miss work to look after sick children or take them to the doctor. These two benefits are correctly treated as benefits of a vaccination program. However, they are just two components of the much wider set of overall benefits that vaccination potentially confers on children, their parents, and their communities.

For example, healthy children have, as mentioned above, better records of school attendance. They also attend school for more years and learn more each year they are enrolled. Vaccinated children also tend to avoid the long-term sequelae associated with certain childhood diseases, such as neurological impairments, hearing loss, and a variety of other physical disabilities. Better educated and healthier than their peers, vaccinated kids will therefore tend to be more productive workers when they grow up.

Such benefits do not only accrue to children. With respect to parents and grandparents, they tend to be healthier themselves if their children and grandchildren are healthy. They also have lower rates of absenteeism, and they avoid the anxiety associated with having children and grandchildren who are ill.

Society also derives benefits from vaccinated, healthy children. These benefits relate first to herd immunity, where even individuals who are not immunized gain protection from disease when other members of the community are immunized.

Immunologists and clinicians express this herd immunity bonus in terms of additional numbers of effectively immunized people; economists focus on the monetary aspects, where those people who avoid illness because of herd immunity will tend to be more productive and require less resources for medical care. Societal benefits also include decreased antibiotic resistance. Because immunization means less need to treat diseases with antibiotics, it decreases the development of antibiotic resistance and the need to resort to what are often far more expensive second-line drugs. Finally, the expectation that children will grow up healthy leads naturally to families having fewer children, a benefit that helps trigger the demographic dividend described above.

The central premise, then, of the new paradigm for the economic evaluation of vaccination is a broad view of the benefits of vaccination, one that incorporates impacts on the many factors listed here, in addition to averted medical care costs and the cost of parental work loss [13]. In other words, if one accepts the argument that "healthier means wealthier," it stands to reason that a proper accounting of the benefits of vaccination must, at a minimum, include the future productivity gains of children who grow up healthier, smarter, and better educated, as well as the economic gains enjoyed by others in their families and communities.

3 Applications of the New Approach

A review of some recent research will demonstrate the kind of results that are produced via the new paradigm for conceptualizing, measuring, and accounting for the full benefits of childhood vaccination. Two studies serve to illustrate the change: one focuses on a Global Alliance for Vaccines and Immunisation (GAVI) program and the other analyzes some data from the Philippines [14].

The GAVI proposal aims to extend the use of a variety of vaccines to 75 low-income countries during 2005–2020, at a cost of US $13 billion. GAVI seeks to expand the traditional basic childhood vaccination package; to increase coverage of the under-used Hib, hepatitis B, and yellow fever vaccines; and to help finance the introduction of vaccines covering meningococcus, pneumococcus, and rotavirus. In principle, this ambitious program will save lives, save medical care costs, and encourage higher labor productivity by supporting the physical and mental development of children. GAVI's epidemiologists estimate that this program will reduce the child mortality rate in the 75 GAVI countries by 4 deaths per 1,000 live births initially (by 2005), and by 12 deaths per 1,000 live births (by the year 2020), a sizable decline.

In an initial, albeit somewhat crude, attempt to estimate the rate of return on this investment, a group of researchers calculated the likely effect of the program on worker productivity at the individual level. The headline result was striking, in which a conservative approach estimated the rate of return on investment in the GAVI immunization program to be 12% by 2005, rising to 18% by 2020. These rates of return compare favorably with rates of return on other highly regarded investments in economic growth and development.

A second study that took a relatively broad view of the benefits of vaccination examined data from the Cebu Longitudinal Health and Nutrition Survey on efforts to immunize children in the Philippines against DTP, TB, polio, and measles. The analysis focused on children's cognitive development and directly links vaccination experience in the first 2 years of life to cognitive function at age 10, as measured by test scores on language, math, and IQ tests.

Using a range of propensity score methods to deal with the problem of non-random assignment, the study found a significant positive effect of childhood vaccination on all three test scores. When international evidence was used to translate those test-score benefits into earnings gains as adults, and to compare those earnings gains to the $20 cost of the vaccine package, another striking result appeared: a 21% rate of return on the vaccine spending.

4 Two Calls to Action

The results of the GAVI study and the Philippines study are at best suggestive. But they both point toward the eminent economic sensibility of immunization programs by virtue of the handsome rate of return they deliver – a return that is higher than previously recognized and that is comparable to estimated rates of return on investments in education, the most exalted instrument of development.

Education economists have long understood that one compelling argument to justify incurring the out-of-pocket and foregone earnings costs of schooling today is the enhancements that schooling yields to productivity and earnings tomorrow.

What the above research suggests is that we acknowledge that the same reasoning applies to spending on vaccination research and coverage. Spending on immunization programs today promotes increased productivity and increased earnings tomorrow – and these increases need to be meaningfully, consistently, and comprehensively measured in the interest of better public and private policy decisions about resource allocation.

Thus, this research potentially provides more than just an incremental contribution to knowledge. It actually has transformative potential: it has the capacity to transform vaccination policy debates from discussions of vaccination programs as burdensome costs into discussions of vaccination programs as income-generating investments. Such a transformation is guaranteed to get the attention of economic policymakers because they are accountable for income growth and poverty reduction. And this can be very fortuitous, since economic policymakers also have the "power of the purse." The first call to action is thus that policymakers, in allocating resources to national vaccination budgets, acknowledge that the rate of return offered by vaccination is likely higher, perhaps considerably, than has been previously thought.

One other certain implication of this research is that the literature on the economic evaluation of vaccination needs to be reconsidered. Most books and articles on the benefits and costs of vaccination discuss only the reduction in healthcare costs

that stem from vaccination, while a few sources also make a passing nod to the benefits of reducing time away from work. As a result, there is much research to be done. The second call to action is directed toward economists and other researchers, who must conduct a new set of benefit–cost analyses, vaccine by vaccine and country by country, to widen and deepen the evidence base regarding the full benefits of vaccination programs.

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Recent Trends in Global Immunisation

Gustav J.V. Nossal

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
	Life expectancy	
Japan	81	86
Australia	79	84
USA	76	81
Afghanistan	41	42
Sierra Leone	39	43
	Deaths under 5 per 1,000 live births	
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–dapsone–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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New Advances in Typhoid Fever Vaccination Strategies

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1 Introduction

Salmonella belong to the group of Enterobacteriaceae that are aerobic, gram-negative rods and approximately 1–3 μm × 0.5 μm in size [1, 2]. Currently there are approximately 2,400 pathogenic species of *salmonella*. *Salmonella* was first identified in 1880 by Eberth from the mesenteric nodes and spleen of a patient dying from typhoid fever [3, 4]. Later in 1884 Gaffky was able to isolate the bacillus. A year later Salmon and Smith described a bacillus that is now known to be *S.* Choleraesuis, the first bacteria that affects both human and animals [5]. *Salmonella* possess a flagellar antigen (H), somatic (O), and a surface antigen Vi. *Salmonella* are divided into two subspecies of *S. enterica* and *S. bongori*. *S. bongori* contains 8 serovars and *S. enterica* contains the other approximately 2,300 serovars that are divided into 6 subspecies based on flagellar H antigen. *Salmonella* nomenclature has undergone many changes [6]. Serotypes of *Salmonella* are recognized using the technique recommended in the Kauffman–White scheme.

Only few *Salmonella* serovars have been identified to cause disease in animals [7]. *Salmonella* subspecies *enterica* serovar Typhi is the most common cause of infection in humans and serologically is placed in *Salmonella* group D due to O antigens 9 and 12 [8]. The genetic makeup of the organism has not shown variation geographically and is stable with a few exceptions of isolates from Indonesia that have slightly different flagellar antigens. *S.* Typhi expresses a polysaccharide capsule Vi (virulence antigen) on its surface and is highly stable serologically compared to other *Salmonella* serotypes [9]. Presence of Vi prevents the binding of O antigen to the O antibody and thus enables the pathogenesis of the organism. Clinical severity of typhoid fever is a result of the Vi antigen that increases the infectivity [10]. However, Vi-negative strains have also been identified; therefore, Vi presence is not essential for *S.* Typhi-related typhoid fever. In vitro studies have shown that the Vi antigen of *S.* Typhi has anti-opsonic and antiphagocytic characteristic that reduces

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the level of secretion of *Salmonella* serovar Typhi-induced tumor necrosis factor alpha (a marker of activation) by human macrophages and increases the level of resistance of the organism to oxidative killing [8].

2 Typhoid Fever Epidemiology

A recent analysis estimated that there are 21 million typhoid fever cases per year and 216,000 deaths [11]. An earlier WHO estimate of the global typhoid disease burden based on a study from 1984 indicated around 17 million cases and approximately 500,000–600,000 deaths per year [11, 12]. Recent analysis assumes an average case fatality rate (CFR) of only 1%, which is at the low end of most estimates in the literature. Typhoid fever is considered endemic in most of the developing world. An estimated 90% of typhoid-related deaths occur in Asia [11, 13].

The recent burden of disease analysis was based on data derived from selected studies in a total of only 10 developing countries that included only one from sub-Saharan Africa (South Africa). High incidence rates of typhoid have been documented for south and Southeast Asia, but arbitrary estimates were made for many regions of the developing world that lacked any data, especially Africa. The paucity of reliable incidence data from most developing countries reflects the fact that laboratories capable of bacteriologic confirmation are lacking in much of the developing world [13]. As well as typhoid fever being endemic, the disease has also appeared as epidemic forms in central Asia, Africa, and south Asia [14].

The incidence of typhoid fever may vary considerably not only between, but also within, countries [15] (Fig. 1). In some countries, evidence suggests that residents of

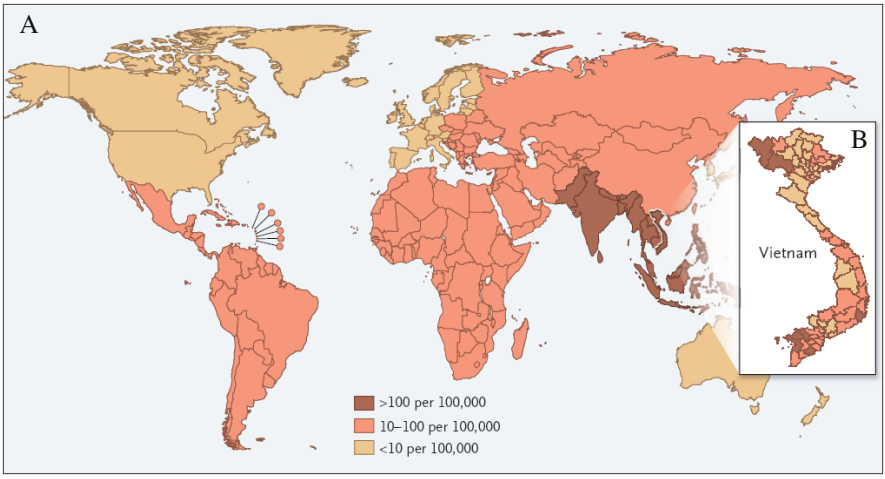

Fig. 1 Estimated distribution of typhoid fever burden in 2000 (a) and the geographic differences of typhoid fever incidence in Vietnam (b) [15]