New Decade of Vaccines 4

The future of immunisation policy, implementation, and financing

Orin S Levine, David E Bloom, Thomas Cherian, Ciro de Quadros, Samba Sow, John Wecker, Philippe Duclos, Brian Greenwood

Vaccines have already saved many lives and they have the potential to save many more as increasingly elaborate technologies deliver new and effective vaccines against both infectious diseases—for which there are currently no effective licensed vaccines—such as malaria, tuberculosis, and HIV and non-infectious diseases such as hypertension and diabetes. However, these new vaccines are likely to be more complex and expensive than those that have been used so effectively in the past, and they could have a multifaceted effect on the disease that they are designed to prevent, as has already been seen with pneumococcal conjugate vaccines. Deciding which new vaccines a country should invest in requires not only sound advice from international organisations such as WHO but also a well informed national immunisation advisory committee with access to appropriate data for local disease burden. Introduction of vaccines might need modification of immunisation schedules and delivery procedures. Novel methods are needed to finance the increasing number of new vaccines that have the potential to save lives in countries that are too poor to afford them. Here, we discuss some options.

Published Online
June 9, 2011
DOI:10.1016/S0140-6736(11)60406-6

See Online/Comment
DOI:10.1016/S0140-6736(11)60765-4,
DOI:10.1016/S0140-6736(11)60766-6, and
DOI:10.1016/S0140-6736(11)60710-1

This is the fourth in a Series of five papers about the new decade of vaccines

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (O S Levine PhD); **Harvard School of Public Health, Harvard University, Cambridge, MA, USA** (D E Bloom PhD); **Immunizations, Vaccines & Biologicals, WHO Headquarters, Geneva, Switzerland** (T Cherian MD, P Duclos PhD); **Sabin Institute, Washington, DC, USA** (C de Quadros MD); **Centre for Vaccine Development, Bamako, Mali** (S Sow MD); **PATH, Seattle, WA, USA** (J Wecker PhD); **and London School of Hygiene and Tropical Medicine, London, UK** (B Greenwood MD)

Correspondence to:
Dr Orin S Levine, International Vaccine Access Center, Department of International Health, Johns Hopkins Bloomberg School of Public Health, 855 N Wolfe Street, Suite 600, Baltimore, MD 21205, USA
olevine@jhsph.edu

Introduction

Since Edward Jenner's breakthrough in 1796, vaccination has probably saved as many lives as any other public health innovation, with the exception perhaps of improvements to sanitation and water safety. Without vaccines, global eradication of smallpox and elimination of poliomyelitis and measles from large parts of the world would have been impossible. These achievements have been accomplished largely with vaccines delivered through a global system, the Expanded Programme on Immunization (EPI), which has received sustained support for more than 30 years from national governments, donor organisations, and international agencies such as UNICEF and WHO. However, diseases such as pneumonia, diarrhoea, meningitis, and measles, which are currently preventable by vaccination, still account for about a quarter of child deaths in low-income countries (figure 1).[1–4] In adults, tuberculosis and cancers of the cervix, liver, and some other sites are also potentially preventable by vaccination and, yet, continue to cause much suffering and many deaths. With these past successes, rapid advances in biomedical sciences, and a delivery system that reaches nearly all children at least once in the first year of life, we have high expectations that new vaccines will further improve global health.

Three major challenges exist to enhancement of current success in prevention of infectious disease by vaccination. First, we need to further expand coverage of existing vaccines, such as those against diphtheria, tetanus, and measles. Second, effective new vaccines need to be implemented widely, such as those against *Haemophilus influenzae* type b and pneumococcal, meningococcal, rotavirus, and human papillomavirus infections. Third, we need to develop new vaccines against important pathogens, such as malaria parasites and HIV, for which no effective licensed vaccine yet exists. Here, in the fourth paper of this Series, we focus mainly on the first and second challenges with respect to low-income and middle-income countries, because these areas are where the main challenges to introduction of new vaccines are found and where characterisation of policies, programmes, and financing necessary for further progress is most urgent. However,

Key messages

- Access to vaccines for children in developing countries began to expand rapidly in the mid-1970s, with establishment of the Expanded Programme on Immunization, and has subsequently prevented many millions of deaths and illnesses
- Immunisation programmes need ongoing review to account for changes in the epidemiology of major infectious diseases and availability of new vaccines
- Vaccination policies should be based on solid evidence and rigorous science; efforts are underway to ensure that all countries have an established body that can make evidence-based decisions about vaccine policy
- Experiences with new vaccines, such as pneumococcal and rotavirus vaccines, have shown that vaccine access for children in developing countries can be accelerated, but this process needs to be improved further to meet the needs of new vaccines on the horizon
- Sustainable predictable financing is likely to be a major ongoing challenge to achievement of universal access to all vaccines; innovative ways are being developed to tackle introduction of pneumococcal and rotavirus vaccines, but financing of other new vaccines, which are likely to be at least as expensive, remains to be established
- Continued vaccine research is needed to keep safe, effective vaccines in the pipeline

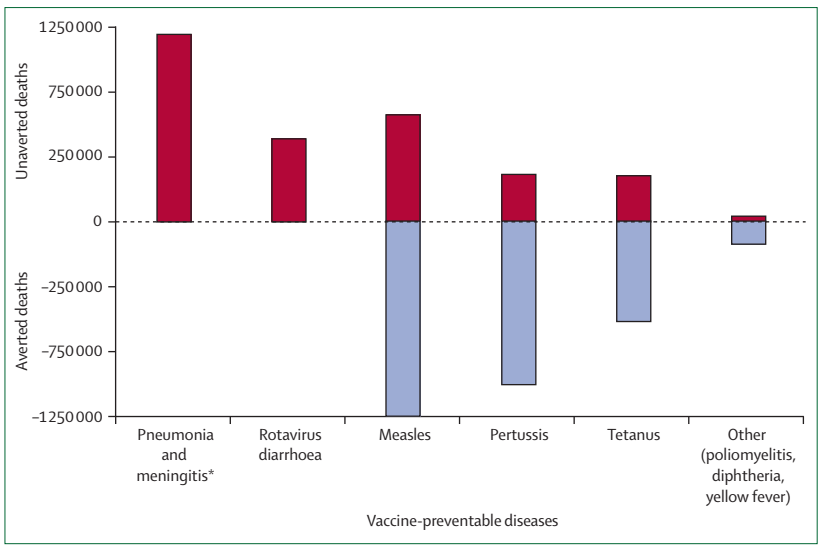


Figure 1: **Global annual estimates of deaths averted and still happening from vaccine-preventable diseases in children younger than 5 years, 2000–04**
Data are taken from Watt,[1] O'Brien,[2] Parashar,[3] Brenzel,[4] and colleagues. *Vaccine-preventable component caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.



Figure 2: **Proportion of children younger than 1 year receiving three doses of diphtheria, tetanus, and pertussis vaccine, 1980–2009**

some issues discussed by us here are also relevant to high-income countries.

Recently developed vaccines, and some of those likely to arrive soon, share many characteristics. In general, they are substantially more complex and expensive than vaccines that preceded them. The new pneumococcal conjugate vaccines, for example, are combinations of ten or 13 individual vaccines and nearly a year is needed to manufacture one batch. Finding ways to ensure that these new vaccines are available and accessible to populations that most need them is a major challenge to the international community.

Origin and evolution of EPI

For a **timeline of World Health Assembly resolutions** see http://www.thelancet.com/series/interactive-vaccines

The foundations of the current global immunisation system can be found in a series of World Health Assembly resolutions starting in 1974. The success of the global smallpox eradication programme, recognition of the enormous potential for vaccination to control communicable diseases, and the fact that in many regions and countries of the world children did not have access to vaccines, led the Assembly to establish the EPI in 1974 (resolution WHA27.57). The first diseases targeted by this programme were diphtheria, pertussis, tetanus, measles, poliomyelitis, and tuberculosis. Global policies for immunisation, and establishment of the goal of providing universal immunisation for all children by 1990, were approved in resolution WHA30.53, adopted in 1977. This goal was deemed an essential element of WHO's strategy to achieve health for all by 2000.

By 1982, concern was raised about the slow progress being made in increasing access to immunisation, and WHO member states were urged to take immediate action. In response to this call, UNICEF and other organisations initiated actions, beginning in 1984, to accelerate immunisation coverage, with the aim of achieving 80% coverage, by 1990, of tuberculosis, combined diphtheria, tetanus, and pertussis, oral polio, and measles vaccines (universal childhood immunisation). This initiative led to rapid increases in immunisation coverage in low-income and middle-income countries, reaching (by 1990) the level of high-income countries in 1980 (figure 2). By 2005, the gap in coverage between countries of low and middle income was erased, but rates remain lower than in high-income countries.

The success of universal childhood immunisation showed that most children and their mothers in less-developed areas could be reached by immunisation services and, therefore, by other primary health-care interventions. However, experience in subsequent years exposed weaknesses in the system and the fragility of the gains. Immunisation coverage stagnated, or even dropped in some countries, as attention was diverted to other areas of health. However, in recent years, with implementation of the Reach Every District strategy, periodic intensification of routine immunisation (which delivers vaccines and other health interventions in a campaign), and provision of additional resources to strengthen immunisation services provided by the GAVI Alliance, further progress has been made. Global immunisation coverage, as measured by the proportion of infants receiving three doses of diphtheria, tetanus, and pertussis vaccine, was estimated at about 82% in 2009.[5]

Although the success of universal childhood immunisation is acknowledged widely, one of its criticisms—and of some disease-control initiatives that have followed it—is that focus on time-bound goals leads to circumvention rather than strengthening of health systems. Addition of disease-control goals was seen as a means to enhance the performance of immunisation programmes and to organise surveillance systems to measure their effect. However, this strategy did not happen in all countries. Evaluations in the 1990s and early 2000s indicated that, in countries where health

systems were working well, universal childhood immunisation and disease-control programmes were very successful (eg, eradication of poliomyelitis in North and South America), whereas universal childhood immunisation proved unsuccessful or unsustainable in countries with weaker health systems.[6]

Key lessons from history include recognition that, as more ambitious goals for immunisation and disease control are set, pressures to meet short-term goals need to be balanced with substantial efforts to establish and sustain strong systems for vaccine delivery, surveillance, and monitoring. Furthermore, the effect of immunisation programmes will be enhanced by their integration as a core component of primary health care, especially since control of diseases targeted by newer vaccines—such as those for pneumonia, diarrhoea, and cervical cancer—require the synergistic action of many approaches to provide maximum success.

Ongoing reviews of social and programmatic determinants of immunisation coverage, programme evaluations to assess the effect of new vaccines, and systematic reviews of publications and grey literature on the effects of vaccine introduction on immunisation and health systems have highlighted some weaknesses and bottlenecks in immunisation programmes in many developing countries.[7] One opportunity to address these issues is the Decade of Vaccines collaboration.[8] The outcome of this collaboration will be a global vaccine action plan that will enable greater coordination across stakeholder groups—national governments, multilateral organisations, civil society, the private sector, and philanthropic organisations—and will identify important policy, resource, and other gaps to realise the lifesaving potential of vaccines.

Efficient and robust immunisation systems, managed and staffed by sufficient numbers of adequately trained health-care workers, should be the basis for achievement of immunisation and disease-control goals. In countries with weak systems, to meet this goal will require that: structures and processes for development of national immunisation policies and plans are strengthened and form the basis of allocation of appropriate financial resources; adequate infrastructure and trained personnel are available to deliver on planned activities; effective and efficient supply systems are in place, which integrate delivery of vaccines and immunisation materials with other health supplies; systems and methods for generation of evidence, monitoring performance, and use of data for action are established; strengths of civil society and the public sector are leveraged to enhance delivery of immunisation; and programmes benefit from sound financial management to ensure financial sustainability.

Global framework for evidence-based immunisation policy

Countries, in particular developing countries, look to WHO for policy recommendations about use of vaccines in their national programmes. To meet this need, WHO solicits recommendations from independent advisory committees, which consist of experts with diverse backgrounds.

The main advisory group to WHO on vaccine policy and strategy is the strategic advisory group of experts (SAGE). Established in 1999 through the merging of two previous committees, SAGE was restructured in 2005. Its activities and modes of operation were then adjusted to suit the requirements of WHO's global immunisation vision and strategy.[9] The remit of SAGE extends to all vaccine-preventable diseases, and the group produces policy and strategy recommendations on use of specific vaccines that form the basis for WHO vaccine position papers. SAGE deliberations take place in a transparent manner during plenary meetings that are open to members of the vaccine community. The open nature of the process extends to public posting of information and evidence that served as the basis for SAGE's decision making.

Since 1998, WHO has regularly produced and updated evidence-based position papers that summarise information on available licensed vaccines, mainly for those used in large-scale immunisation programmes. The process for preparation of papers has been improved over time. The latest addition is inclusion of tables that assess and grade quality of evidence, using the GRADE (grading of recommendations assessment, development and evaluation) approach.[10] Position papers are prepared in English, published in English and French in the *Weekly Epidemiological Record*, and made available in the other four official languages of WHO—ie, Arabic, Chinese, Russian, and Spanish.

For more on the ***Weekly Epidemiological Record*** see http://www.who.int/wer/en

Several technical advisory committees complement SAGE by providing independent policy recommendations related to vaccines. The main groups are the global advisory committee on vaccine safety, the expert committee on biological standardisation, the immunisation practice advisory committee, and the quantitative immunisation and vaccine research advisory committee.

Global recommendations are reviewed and adapted at regional level by technical advisory groups of every WHO regional office, and at country level by national policy-making bodies. Global and regional policy recommendations, therefore, need to be flexible and not prescriptive so that they allow national bodies the autonomy to make policies on the basis of local epidemiological and programmatic considerations and competing health priorities. Most industrialised—and an increasing number of developing—countries have established national technical advisory bodies (generally referred to as national immunisation technical advisory groups) to guide their immunisation policies, but only 30% of least-developed countries currently have such groups and, therefore, WHO and others are working to help establish them.[11,12]

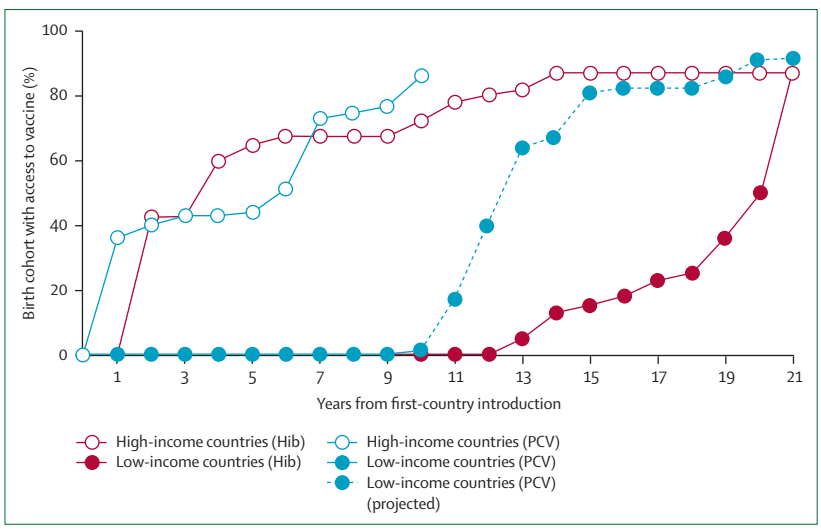


Figure 3: **Uptake of Hib and pneumococcal vaccines in high-income versus low-income countries**
Hib=*Haemophilus influenzae* type b. PCV=pneumococcal vaccine. Dashed line=projected uptake. Solid line=actual uptake.

In recent years, WHO has improved the rigour and transparency of processes it uses to recommend use of vaccines in national policies. However, events and trends show a need for continued strengthening of practices at the highest level and, more importantly, expansion and improvement of national policy-making bodies and procedures. Allegations[13] of undue influence by manufacturers of influenza vaccines indicate a need for WHO to continuously monitor the involvement of industry, and industry-sponsored experts, in its policy processes and to communicate clearly those roles to external audiences.

To create sustainable financing and policy for vaccines, much more must be done to generate complementary decision-making capacity in developing countries themselves. Although WHO helps developing countries with limited policy capacity or expertise by critically reviewing vaccines and establishing evidence-based policies for vaccine use, it is not in a position to rank or prioritise use of many vaccines in a given country. This scenario—prioritising several recommended vaccines—is increasingly common in low-income and middle-income countries and falls squarely on the countries themselves, who are best positioned to assess local epidemiological, programmatic, and financial effects of decisions. Success in this area is vital, even if in some cases it leads to heterogeneity in vaccine prioritisation within regions, and perhaps to differences between countries and WHO. As long as decisions are evidence-based and locally owned, these policies should be embraced and supported.

Introduction of vaccines into national programmes

Historically, in wealthy countries with low mortality, new vaccines were incorporated rapidly into programmes, whereas in countries with the highest burden of disease, uptake was delayed by 15–20 years.[14] The inequity represented by this paradoxical situation has led to enhanced efforts to better understand the drivers of new vaccine adoption in national programmes and to accelerate the process.

Research and past experience show that national policy makers need a set of key data and information to make a decision about policy related to vaccine introduction and that, in the past, important evidence sometimes did not reach key policy makers in a timely and effective manner. For example, policy makers indicate consistently that their decisions require data for the burden of vaccine-preventable disease, the vaccine's efficacy and safety, and the cost-effectiveness of vaccination, but rarely make the investments needed to generate these data. In the past, even when these data were published in peer-reviewed journals, they did not reach policy makers. Furthermore, no matter how compelling the data for disease burden or a vaccine's efficacy, financing of newer vaccines (which cost more than traditional EPI vaccines), both in the immediate and longer term, was a major obstacle for many low-income and middle-income countries.[15,16] The early experience of the GAVI Alliance showed that, with *H influenzae* type b conjugate vaccines, overcoming the financial obstacle alone—by providing free vaccine—was not sufficient to stimulate widespread national demand and both evidence and financing had to be in place.[17]

In an effort to accelerate the vaccine introduction process in low-income countries, the GAVI Alliance created accelerated development and introduction plans for pneumococcal and rotavirus vaccines in 2003 and the Hib initiative for *H influenzae* type b vaccine in 2005.[18–20] These programmes were tasked with generation and communication of evidence on these vaccines and the diseases they prevent, to support policy processes at global, regional, and local levels.[21,22] By identification of information gaps and filling of them simultaneously, these two programmes were able to provide a comprehensive body of evidence—including epidemiological findings, data for vaccine efficacy, demand forecasting, and financing needs—that helped to support decision making at all levels. Figure 3 shows that the projected rollout of pneumococcal vaccines in low-income countries will be substantially faster than historical precedents with *H influenzae* type b conjugate vaccines. For a modest investment, the pneumococcal and rotavirus accelerated development and introduction plans and the Hib initiative have succeeded in hastening uptake of these new vaccines; even 1 year of accelerated uptake represents many young lives saved. Critics of these programmes, while recognising their successes, have suggested that by focusing on one vaccine, these programmes could have inadvertently created the appearance of competition among diseases, and to have three separate groups instead of just one integrated

programme was inefficient. Evidence for this criticism is scarce, but creation by the GAVI Alliance of a new structure, the accelerated vaccine initiative, with responsibility for hastening uptake of all new vaccines, is a rational response.

Practical challenges

Although the current EPI system provides a fairly robust platform for vaccine delivery in most countries, new vaccines sometimes present practical and logistical challenges. In recent times, challenges have been driven by poor packaging and presentation for use in the EPI system in developing countries. For example, introduction of the first pneumococcal conjugate vaccines posed challenges with safe handling and disposal of prefilled syringes. These syringes were made of glass, and many developing countries do not have the incinerator capacity to destroy glass syringes effectively outside main cities, a drawback that was not considered when plans for rolling out pneumococcal immunisation were first made. Although short-lived, this constraint probably delayed initial uptake of the vaccine in a few countries. Challenges could also be related to delivery requirements of the vaccines themselves, as in the case of rotavirus vaccine implementation, for which age windows are recommended for administration of the first and last doses to minimise risk of intussusception. Since new vaccines come with novel presentations and delivery schedules, practical implications of delivery must be considered well in advance, and health workers should be trained to deliver the vaccine safely and successfully.

Many new vaccines prevent some, but not all, causes of a particular clinical syndrome. As a result, social mobilisation and community education programmes are needed to avoid misunderstandings and frustrations later on when people continue to present with diseases not covered by the vaccine. For example, a new meningococcal conjugate vaccine has been successfully rolled out in Burkina Faso, Mali, and Niger with wide publicity[23] and very high vaccine coverage. However, it prevents only one form of meningococcal meningitis (serogroup A) and outbreaks caused by other serogroups are likely in these countries in the next few years. Without careful planning and ongoing education of the community, subsequent outbreaks could be misunderstood and, hence, jeopardise popular trust in other vaccines and programmes.

Although challenges associated with new vaccines can place additional strain on the EPI system as it adapts to them, opportunities exist for new technologies to help ease this transition in the future. Novel technologies could affect everything from how we store and deliver new or existing vaccines to how we adapt schedules to accommodate new vaccines. Vaccine stabilisers, aerosolised vaccines, or intradermal patches could improve effectiveness of existing vaccines and immunisation programmes or provide breakthroughs in vaccination against diseases such as HIV or tuberculosis, for which safe effective vaccines are not yet available. Mobile telephones, for example, could be useful for improving the timeliness of vaccination by sending reminders to parents or for providing precise and timely information on vaccine stockouts in remote clinics. For each of these advances, policy makers will need to examine carefully all the facts, including expected benefits and costs and programmatic implications.

Post-vaccination surveillance

As new vaccines are introduced, high-quality surveillance becomes imperative to monitor a vaccine's effects, especially for diseases for which substantial antigenic diversity exists.[24,25] Without local surveillance to establish the ongoing benefit of a vaccine, evidence of an effect will be impossible to show; however, costs and side-effects are easily quantified. If data for disease effect are absent, maintenance of political support for the vaccine programme can become difficult. Importantly, not all surveillance is equally helpful. Poor-quality surveillance could lead to inferences that a vaccine is not working, even if it is, and thereby support for a successful programme could be jeopardised.

Continued surveillance to monitor the effect of vaccine programmes is essential for diseases whose causative organism shows antigenic diversity, such as pneumococcus and rotavirus. Replacement of serotypes of pneumococci included in polyvalent conjugate vaccines by those not part of the vaccine has already been recorded in some places where these vaccines have been introduced, and surveillance for changes in prevalent strains will be essential after introduction of vaccines against rotavirus and against pneumococcal and other infectious diseases.[26] Introduction of vaccines that are only partly effective, or that provide only a short period of protection, could change the epidemiological pattern of an infection and, hence, the approach adopted by the health services to control it. For example, introduction of a malaria vaccine that gives only a short period of protection in the routine EPI system, as might happen in the next few years, would be likely to shift the burden of malaria from young to older children, necessitating different approaches to management of this infection.

Vaccine use can also affect empirical treatment algorithms.[27] Widespread deployment of *H influenzae* type b and pneumococcal conjugate vaccines will not only reduce the number of severe pneumonia cases seen in health facilities but also make the relative contribution of other causes more relevant. These changes in causal patterns will require changes in treatment algorithms and empirical treatments. More research projects, such as the Pneumonia Etiology Research for Child Health study that is underway in seven developing countries, are needed to help inform a new evidence base for establishment of treatment policies.

	Definition
Narrow perspective	
Health gains	Reduction in mortality and morbidity through vaccination
Health-care cost savings	Savings of medical expenditure because vaccination prevents episodes of illness
Care-related productivity gains	Savings of parents' productive time because vaccination avoids the need to take care of a sick child
Broad perspective	
Outcome-related productivity gains	Increased productivity because vaccination improves cognition and physical strength, as well as school enrolment, attendance, and attainment
Behaviour-related productivity gains	Benefits accrued because vaccination improves child health and survival and thereby changes household behaviour
Community external factors	Benefits accrued because vaccination improves outcomes in unvaccinated community members

Adapted from Bärnighausen and colleagues,[30] with permission of the *South African Medical Journal*.

Table 1: **Benefits in economic evaluations of childhood vaccinations**

	US price per dose (US$)		Weighted average price per dose (US$)	
	CDC (public)	CDC (private)	UNICEF for GAVI Alliance*	PAHO revolving fund†
DTwP-Hib (liquid, ten doses per vial)	N/A	N/A	3·40	3·30
DTwP-HepB-Hib (pentavalent vaccine; liquid, one dose per vial)	N/A	N/A	3·01	3·20
Hib (lyophilised, one dose per vial)	N/A‡	N/A	3·40	2·25
Pneumoccocal conjugate ten-valent (liquid, one or two doses per vial)	N/A	N/A	7·00	20·00
Pneumococcal 13-valent (liquid, one dose per vial or prefilled syringe)	91·75	114·15	7·00	20·00
Rotavirus (liquid, two-dose schedule)	83·75	102·50	N/A	7·50
Rotavirus (liquid, three-dose schedule)	59·18	69·59	N/A	5·15

CDC=Centers for Disease Control and Prevention. PAHO=Pan American Health Organization. DTwP=diphtheria, tetanus, and whole-cell pertussis. Hib=*Haemophilus influenzae* type b. HepB=hepatitis B. Data are taken from the International AIDS Vaccine Initiative,[35] CDC,[36] UNICEF,[37] and PAHO.[38] All vaccines are recommended for a three-dose schedule, unless stated otherwise. *Pneumococcal prices based on advance market commitment terms of price per dose $3·50 plus $3·50 subsidy. †PAHO price does not specify which pneumococcal conjugate vaccine it is purchasing for $20·00 per dose but does indicate that it is a single-dose formulation. ‡The USA offers the Hib vaccine (liquid, ten pack, one-dose vials) for $11·51 per dose (public) and $22·77 per dose (private).

Table 2: **Prices of selected vaccines, 2010**

Finally, because many new vaccines are introduced within a fairly brief period, stronger pharmacovigilance systems are needed that can accurately capture potential adverse events associated with all antigens.[28] Thus, new vaccines provide an opportunity to strengthen surveillance both for adverse events after immunisation and for the vaccine-preventable illness itself. In this way, surveillance helps to maintain public confidence in immunisation and public health systems.

Capturing the full benefits of vaccination

Health decision makers have an opportunity to make important strides to increase child survival. Estimates suggest that vaccines avert more than 2·5 million child deaths a year and, if vaccine coverage was increased, prevention of up to 2 million additional deaths per year might be possible (figure 1). In addition to political factors, decision makers consider costs and benefits when setting health-system priorities. The traditional view of benefits includes forestalled costs of medical care and reduced time costs of caretaking. However, research into links between population health and economic development suggests that the benefits of vaccination go well beyond these categories.[29–31]

The broader view of vaccination's benefits includes productivity gains and externalities (table 1). Increases in productivity arise as a result of improvements in cognition, physical strength, and school attendance and attainment associated with avoidance of vaccine-preventable disease. For example, diarrhoeal disease can lead to stunting in children, and *H influenzae* type b and pneumococcal meningitis can lead to permanent disability, such as hearing loss or developmental delays.[32–34] Avoidance of these sequelae helps children become productive adults.

Furthermore, from a household perspective, not all health expenditures affect families equally: some are easily manageable whereas others represent a catastrophic health expense that could drive a family into debt and retard their ability to climb out of poverty. Some diseases that are preventable by vaccine (or will be in the near future) can be particularly associated with such catastrophic health expenses (eg, meningitis, pneumonia, malaria, dengue haemorrhagic fever). Prevention of these types of expenses by vaccination could potentially have an important effect on helping to interrupt the cycle of poor health to poverty to poor health.

Childhood vaccination can also promote improvements in economic wellbeing through the effects of improved child health and increased child survival on fertility, and yet these benefits are rarely captured in assessments of the benefits of vaccination. For example, in areas with high rates of child mortality, parents might choose to have many children to ensure that the desired number survive to adulthood. Improved child survival, therefore, can help families achieve their desired size through fewer pregnancies and births. Also, with fewer children, parents can devote more resources (eg, nutrition, health, education) to every child, which can in turn improve child development and future productivity. Childhood vaccination can also confer benefits to the community, insofar as it promotes herd immunity and slows the pace at which antibiotic resistance develops.

Financing vaccines now and in the future

Financing new vaccines represents a major challenge for all global and national programmes. Prices for new vaccines—such as those against rotavirus and pneumococcal disease—are high compared with those for traditional vaccines, and health ministries in many countries are struggling to accommodate the costs (table 2). The same is true for new adolescent and adult vaccines,

 Published online June 9, 2011 DOI:10.1016/S0140-6736(11)60406-6

such as the human papillomavirus vaccine, which can cost upwards of US$130 for each of the recommended three doses in some countries. In the USA, the cost to fully vaccinate a child has risen from $155 in 1995 to $1170 in 2007, and reimbursement and insurance schemes have left up to 14% of the country's children underinsured for all vaccines.[39,40] In developing countries, challenges are even more stark. Many African countries are currently struggling to find about $0·50 per dose to purchase a new meningococcal serogroup A conjugate vaccine for prevention of epidemic meningitis and are asking donors to support this vaccine's cost.

Why are new vaccines much more expensive than existing ones? Production costs are relatively high owing to expensive technologies such as conjugation methods and the need for complex adjuvants. These costs are magnified by the need to recover expenditure from other failed research and development efforts and because of profit margins that reflect monopoly patent protections.

Several innovative mechanisms have been established to finance more widespread childhood vaccination (panel 1). These apply various strategies—some in combination—to achieve greater access to affordable sustainable supplies of quality vaccines. The mechanisms also work with one another, with the GAVI Alliance central to many. The GAVI Alliance pools resources from donors to finance the expansion of safe effective vaccine systems and accelerate new vaccine introduction, and its board coordinates investments in a strategic manner. For fundraising, it uses various approaches, including traditional direct-to-donor fundraising and innovative approaches such as the international finance facility for immunisation (which securitises future funding pledges on the international bond market to create sizeable upfront financing) and the advance market commitment (which pools funding for a vaccine in advance of its licensure to bring about better vaccines and better prices for developing countries). For procurement, the GAVI Alliance provides funds to UNICEF or the Pan American Health Organization, which provide pooled acquisition of vaccines and supplies for nearly all the world's poorest countries. Although successful in the past decade, the GAVI Alliance currently faces a serious funding challenge, with a gap of up to $4 billion needed by 2015. In the current economic climate in donor countries, all aid funding—including for the GAVI Alliance—is scrutinised increasingly, and successful replenishment is by no means going to be easy to accomplish.

Technology transfer, in which the capacity to produce new vaccines locally is developed, is another approach available to countries of low and middle income where vaccine manufacturing and well-functioning regulatory agencies exist and large domestic populations make transaction costs worthwhile. Similarly, product development partnerships offer the opportunity to draw on practices of organisations in both the public and private sectors and could speed development of vaccines for which the commercial market is small or uncertain and, hence, less desirable for private companies on their own.

Financing issues are probably most complicated and difficult for the segment of countries regarded as lower middle income, and especially those just above the threshold for GAVI Alliance eligibility. According to the

Panel 1: **Innovative mechanisms to overcome financing obstacles to immunisation**

Pooled financing and improved coordination

GAVI Alliance

In low-income and middle-income countries, the GAVI Alliance—a public-private global-health partnership—aims to increase access to immunisation by providing support in five major areas: immunisation services; new and underused vaccines; injection safety; health-system strengthening; and civil society organisation

Innovative financing

IFFIm

IFFIm is a funding mechanism through which long-term, legally binding commitments are made by donors to support the sale of long-term bonds in international capital markets; sale of these bonds provides cash that can be used by the GAVI Alliance and, so far, IFFIm has raised US$2 billion

AMC

AMC is another financing mechanism aimed at expanding development and availability of vaccines in low-income and middle-income countries; the first-ever AMC was launched in 2007 for pneumococcal vaccine by the governments of Canada, Italy, Norway, Russia, and the UK, the Bill & Melinda Gates Foundation, the GAVI Alliance, and the World Bank, with an investment of US$1·5 billion

Pooled procurement

PAHO revolving fund

The PAHO revolving fund for vaccine procurement uses bulk purchasing to secure vaccines, syringes, and cold-chain supplies for 38 countries in Latin America and the Caribbean; PAHO acts as the purchasing agent for participating countries, who repay the fund along with a small fee, and in 2010, the fund offered 46 types of vaccines to participating countries, for a projected total of 155 million doses, at a value of $320 million

UNICEF

The UNICEF supply division purchases vaccines and vaccine supplies on behalf of nearly all low-income countries; in 2009, UNICEF procured nearly 3 billion vaccine doses valued at more than $800 million, and more than $60 million in vaccine supplies

Supply-side approaches

Technology transfers

Middle-income countries are already home to many vaccine manufacturers that provide traditional vaccines and, increasingly, they are using their large populations to expand their capacity to produce new vaccines—eg, Brazil has agreed to purchase about $2·2 billion of GlaxoSmithKline's vaccine for pneumococcal disease over an 8-year period, in exchange for technology transfer, eventually allowing Brazil to manufacture the vaccine itself

Product development partnerships

Product development groups, usually in the not-for-profit sector, can help to stimulate research and product development without passing on the need for profits or other expenses; several vaccines have been or are being developed in this manner, including candidate vaccines against HIV/AIDS, tuberculosis, malaria, diarrhoea, pneumonia, and meningitis

IFFIm=International Finance Facility for Immunisation. AMC=advance market commitment. PAHO=Pan American Health Organization.

World Bank, countries with a gross national income per person of between $996 and $3945 in 2009 are classified as lower middle income, a grouping that includes nations of staggering diversity—from the tiny Marshall Islands and Cape Verde to economic and population giants such as China, Pakistan, Nigeria, and Indonesia. GAVI Alliance eligibility (restricted to countries with a gross national income per person of <$1500) triggers international financial support for vaccine purchases and systems and (sometimes) access to preferential prices, both of which can diminish financial obstacles to vaccine procurement and delivery. As a result, lower middle-income countries just over the GAVI Alliance eligibility threshold are left out of these financing and pricing schemes. In the open market, these countries generally fare less well than nations with either low or high incomes. When faced with having to pay the same prices as wealthier countries, but with less national wealth, the financial implications of vaccine procurement can be a major obstacle to uptake. This factor is especially important for small countries, which cannot use large volumes to leverage price discounts.

Middle-income countries must be a major focus of efforts to assure access to vaccines in this decade. Unlike 20 years ago, when 90% of the world's poorest people lived in low-income countries, most of the world's impoverished individuals are now living in middle-income countries. This observation has implications for both international aid policies and for how much focus is given to improvement of national policies in these countries to enhance distribution of resources. Resolution of financing issues for middle-income countries might also affect sustainability of financing for low-income countries through the GAVI Alliance. For example, if lower prices meant that more countries would finance their programmes with national funds, then fewer countries would need GAVI Alliance support and donors would be better able to sustain the GAVI Alliance's funding.

The role of research

Development of new vaccines requires research in many disciplines, as reviewed in the first paper in this Series.[41] Successful licensure of a new vaccine signals the beginning of a phase of research, not the end. Operational research that supports optimum deployment of vaccines is not always scientifically glamourous but is essential to maximise returns after application of time and funds needed to develop and license a new vaccine. Operational research can help identify either the best immunisation strategy for deployment of new vaccines in different countries—or within subregions of the same country—or ways to improve the efficiency of delivery systems.

The immunisation dosing schedule currently in use across the world was established to deliver effectively a few vaccines in the first year of life. The programme's schedule was designed as a balance of logistical, epidemiological, and immunological factors, but had little experimental research to guide it. As more vaccines are added to this programme, with different immunological characteristics and target diseases, the recommended schedule must be kept under continuous review—a process currently undertaken by WHO—to ensure that new vaccines are introduced in a way that is immunologically sound and that does not cause practical difficulties for those administering them. In the next few years, new routine schedules are likely to be recommended, and these will need continuous updating as new vaccines, and perhaps new methods of delivery of vaccines (such as intradermal immunisation), come along. 10 years hence, routine immunisation schedules could be rather different from those in use today.

Post-licensure research on issues such as modification of implementation schedules to meet local epidemiological patterns needs financial support, but funding this kind of research does not fit readily into the mandate of any major donor. The same situation applies to disease and microbiological surveillance after introduction of a vaccine. As discussed above (see post-vaccination surveillance), surveillance after vaccination—including detailed microbiological monitoring—is essential when new vaccines directed against a polymorphic organism (such as pneumococcus, rotavirus, or the malaria parasite) are introduced into routine immunisation programmes, to detect any vaccine-induced serogroup or serotype replacement. Research of this kind—eg, measuring the effect of a pneumococcal conjugate vaccine of limited valency on serotype distribution of pneumococci that lead to carriage and invasive pneumococcal disease, which is currently being undertaken in The Gambia—is expensive and not likely to be financed by the vaccine manufacturer once an established market has been achieved, and it might not be as attractive to traditional funders of academic research as new discoveries are. National EPI systems in developing countries do not usually have the resources to undertake applied research or disease surveillance. Thus, in developing nations, research of this type needs to be supported by the international health community and agencies, including WHO, that are likely to use this information. Agencies such as WHO currently do not have the resources (financial and otherwise) to support these types of projects, making this funding gap important and in need of urgent attention.

Here, we have focused mainly on challenges to vaccination against infectious disease. However, the scope of preventive vaccines continues to expand. Vaccine candidates have been developed for prevention or management of hypertension, diabetes, asthma, addiction, and Alzheimer's disease, and for the treatment of cancer. If an increasing number of effective vaccines

 Published online June 9, 2011 DOI:10.1016/S0140-6736(11)60406-6

Panel 2: Call for action

- Strengthen delivery systems to reach all age-groups (infants, adolescents, and adults) by improvement of human resources, financial management, and information and supply systems
- Improve surveillance of health outcomes and adverse events to maintain public confidence and political and financial support for new immunisation programmes
- Establish strong policy processes at national level to make sound local decisions on vaccine introduction and deployment
- Undertake research to capture the full economic benefits of immunisation and to optimise the schedules and delivery of vaccines
- Assure sufficient financing for universal access to all vaccines by concerted coordinated efforts and with special focus on issues facing middle-income countries

directed at prevention or management of chronic diseases emerge, major challenges will arise with respect to establishing how they can best be used. How will these vaccines be delivered? Will they be targeted at solely high-risk groups? How will these people be identified? Development of vaccines against chronic diseases could be viewed chiefly as an issue of importance to developed countries, but as the epidemics of obesity, hypertension, and diabetes spread across the developing world, in the future, vaccines against these disorders could play as important a part in prevention of morbidity and mortality as vaccines against infectious diseases do today. How can vaccines against non-infectious diseases be implemented and financed in the developing world? We will need new streams of research and proactive efforts to anticipate changes needed to existing policy, financing, and delivery systems.

Conclusions

Nearly 40 years after inception of EPI, the global immunisation system must prepare for a new decade of vaccines with unique challenges in terms of expanding surveillance for new diseases, financing development of more expensive vaccines, and increasing coverage of existing and new vaccines (panel 2). Several improvements at global level provide new capacity to support timely development of evidence-based global policies and to disseminate these to a growing number of capable local and regional policy-making organisations. Financing of new vaccines and systems for their delivery are stronger than ever before but have more challenges. A robust pipeline of new yet generally more expensive vaccines is coming, and relevant expansions for delivery, surveillance, and monitoring systems at local level are needed to ensure they are safely, swiftly, and effectively delivered to everyone who needs them.

Contributors

All authors contributed to writing of the report.

Conflicts of interest

TC and PD are employees of WHO. JW and OSL are supported by grants from the GAVI Alliance and the Bill & Melinda Gates Foundation. JW has received travel expenses from GlaxoSmithKline. All other authors declare that they have no conflicts of interest.

Acknowledgments

TC and PD are staff members of WHO; however, the views expressed in this paper are personal views and may not necessarily reflect the official policies or position of the organization. We thank Marta Gacic-Dobo (WHO) and Ryan Fongemie (Johns Hopkins Center for Teaching and Learning with Technology) for assistance with preparation of figures and graphics; and Elizabeth Cafiero (Harvard University) for assistance with research. © World Health Organization, 2011.

References

1 Watt JP, Wolfson LJ, O'Brien KL, et al, and for the Hib and Pneumococcal Global Burden of Disease Study Team. Burden of disease caused by *Haemophilus influenzae* type b in children younger than 5 years: global estimates. *Lancet* 2009; **374:** 903–11.

2 O'Brien KL, Wolfson LJ, Watt JP, et al, and for the Hib and Pneumococcal Global Burden of Disease Study Team. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009; **374:** 893–902.

3 Parashar UD, Burton A, Lanata C, et al. Global mortality associated with rotavirus disease among children in 2004. *J Infect Dis* 2009; **200** (suppl 1): S9–15.

4 Brenzel L, Wolfson LJ, Fox-Rushby J, Miller MA, Halsey NA. Vaccine preventable diseases. In: Jamison DT, Breman JG, Measham AR, et al, eds. Disease control priorities in developing countries, 2nd edn. New York, NY: Oxford University Press, 2006: 389–412.

5 Centers for Disease Control and Prevention. Global routine vaccination coverage, 2009. *MMWR Morb Mortal Wkly Rep* 2010; **59:** 1367–71.

6 Loevinsohn B, Aylward B, Steinglass R, Ogden E, Goodman T, Melgaard B. Impact of targeted programs on health systems: a case study of the polio eradication initiative. *Am J Public Health* 2002; **92:** 19–23.

7 WHO. Meeting of the Strategic Advisory Group of Experts on immunization, October 2009: conclusions and recommendations. *Wkly Epidemiol Rec* 2009; **84:** 517–32.

8 Bill & Melinda Gates Foundation. Global health leaders launch Decade of Vaccines collaboration. Dec 2, 2010. http://www.gatesfoundation.org/press-releases/Pages/decade-of-vaccines-collaboration.aspx (accessed March 31, 2011).

9 Bilous J, Eggers R, Gasse F, et al. A new global immunisation vision and strategy. *Lancet* 2006; **367:** 1464–66.

10 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:** 924–26.

11 Bryson M, Duclos P, Jolly A, Cakmak N. A global look at national Immunization Technical Advisory Groups. *Vaccine* 2010; **28** (suppl 1): A13–17.

12 Senouci K, Blau J, Nyambat B, et al. The Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) initiative: a country-driven, multi-partner program to support evidence-based decision making. *Vaccine* 2010; **28** (suppl 1): A26–30.

13 Cohen D, Carter P. WHO and the pandemic flu "conspiracies". *BMJ* 2010; **340:** c2912.

14 Levine OS, Knoll MD, Jones A, Walker DG, Risko N, Gilani Z. Global status of *Haemophilus influenzae* type b and pneumococcal conjugate vaccines: evidence, policies, and introductions. *Curr Opin Infect Dis* 2010; **23:** 236–41.

15 Wenger JD, DiFabio J, Landaverde JM, Levine OS, Gaafar T. Introduction of Hib conjugate vaccines in the non-industrialized world: experience in four 'newly adopting' countries. *Vaccine* 1999; **18:** 736–42.

16 Watt JP, Levine OS, Santosham M. Global reduction of Hib disease: what are the next steps? Proceedings of the meeting Scottsdale, Arizona, September 22–25, 2002. *J Pediatr* 2003; **143** (6 suppl): S163–87.

17 Shearer JC, Stack ML, Richmond MR, Bear AP, Hajjeh RA, Bishai DM. Accelerating policy decisions to adopt *Haemophilus influenzae* type B vaccine: a global, multivariable analysis. *PLoS Med* 2010; **7:** e1000249.

18 Levine OS, Cherian T, Shah R, Batson A. PneumoADIP: an example of translational research to accelerate pneumococcal vaccination in developing countries. *J Health Popul Nutr* 2004; **22:** 268–74.

19 Wecker JR, Phillips DC, Hayes J. Rotavirus vaccines: the role of researchers in moving evidence to action. *Vaccine* 2009; **27** (suppl 5)**:** F4–6.

20 Hajjeh RA, Privor-Dumm L, Edmond K, et al. Supporting new vaccine introduction decisions: lessons learned from the Hib initiative experience. *Vaccine* 2010; **28:** 7123–29.

21 Levine OS, Hajjeh R, Wecker J, et al. A policy framework for accelerating adoption of new vaccines. *Hum Vaccin* 2010; **6:** 1021–24.

22 Clemens J, Holmgren J, Kaufmann SH, Mantovani A. Ten years of the Global Alliance for Vaccines and Immunization: challenges and progress. *Nat Immunol* 2010; **11:** 1069–72.

23 WHO. Revolutionary new meningitis vaccine set to wipe out deadly epidemics in Africa. Dec 6, 2010. http://www.who.int/mediacentre/news/releases/2010/meningitis_20101206/en/index.html (accessed March 30, 2011).

24 Knoll MD, Moisi JC, Muhib FB, et al. Standardizing surveillance of pneumococcal disease. *Clin Infect Dis* 2009; **48** (suppl 2)**:** S37–48.

25 Widdowson MA, Steele D, Vojdani J, Wecker J, Parashar U. Global rotavirus surveillance: determining the need and measuring the impact of rotavirus vaccines. *J Infect Dis* 2009; **200** (suppl 1)**:** S1–8.

26 WHO. Changing epidemiology of pneumococcal serotypes after introduction of conjugate vaccine: July 2010 report. *Wkly Epidemiol Rec* 2010; **85:** 434–36.

27 Scott JA, English M. What are the implications for childhood pneumonia of successfully introducing Hib and pneumococcal vaccines in developing countries? *PLoS Med* 2008; **5:** e86.

28 Bines JE, Patel M, Parashar U. Assessment of postlicensure safety of rotavirus vaccines, with emphasis on intussusception. *J Infect Dis* 2009; **200** (suppl 1)**:** S282–90.

29 Bloom DE, Canning D, Weston M. The value of vaccination. *World Econ* 2005; **6:** 15–39.

30 Bärnighausen T, Bloom DE, Canning D, O'Brien J. Accounting for the full benefits of childhood vaccination in South Africa. *S Afr Med J* 2008; **98:** 842–46.

31 Bärnighausen T, Bloom DE, Canning D, et al. Best practice paper: the economic case for expanding vaccination coverage of children. 2009. http://www.copenhagenconsensus.com/Default.aspx?ID=1308 (accessed March 30, 2011).

32 Ramakrishnan M, Ulland AJ, Steinhardt LC, Moisi JC, Were F, Levine OS. Sequelae due to bacterial meningitis among African children: a systematic literature review. *BMC Med* 2009; **7:** 47.

33 Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10:** 317–28.

34 Edmond K, Dieye Y, Griffiths UK, et al. Prospective cohort study of disabling sequelae and quality of life in children with bacterial meningitis in urban Senegal. *Pediatr Infect Dis J* 2010; **29:** 1023–29.

35 International AIDS Vaccine Initiative. Procurement and pricing of new vaccines for developing countries. August, 2008. http://www.iavi.org/publications-resources/pages/PublicationDetail.aspx?pubID=af228b16-948c-4ca0-bfeb-caf2f6122055 (accessed April 7, 2011).

36 Centers for Disease Control and Prevention. CDC vaccine price list. http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm (accessed March 20, 2011).

37 UNICEF. Product menu for vaccines supplied by the UNICEF for the GAVI alliance. May 31, 2010. http://www.unicef.org/supply/files/Product_Menu_update_31_May.pdf (accessed April 7, 2011).

38 Pan American Health Organization. PAHO revolving fund: vaccine and syringe prices, 2010. February, 2010. http://www.paho.org/english/ad/fch/im/sne3201.pdf (accessed April 4, 2011).

39 Lee GM, Santoli JM, Hannan C, et al. Gaps in vaccine financing for underinsured children in the United States. *JAMA* 2007; **298:** 638–43.

40 Lindley MC, Shen AK, Orenstein WA, Rodewald LE, Birkhead GS. Financing the delivery of vaccines to children and adolescents: challenges to the current system. *Pediatrics* 2009; **124** (suppl 5)**:** S548–57.

41 Moxon ER, Siegrist C-A. The next decade of vaccines: societal and scientific challenges. *Lancet* 2011; published online June 9. DOI:10.1016/S0140-6736(11)60407-8.