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"Our call to action for the new decade of vaccines embraces four key elements: intensified research and development; advocacy at the highest level; increased shouldering of responsibilities by developing countries; and an expanded effort in communicating benefits of vaccines."

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The vaccine paradox

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The next decade will likely bring astonishing successes in vaccine biology, discovery, and delivery. Justifiable confidence in this proposition led the Bill & Melinda Gates Foundation last year to pledge US$10 billion to a new Decade of Vaccines. For the world's largest and most influential health foundation, vaccines are the number one priority. The foundation estimates that if vaccine coverage could be scaled up to 90%, the lives of 7·6 million children younger than 5 years could be saved between 2010 and 2019. If a malaria vaccine became available by 2014, this figure could rise by a further 1·1 million.

To address the opportunity the Gates Foundation has identified, we brought together some of the leading scientists working in vaccines today to set out the hopes and possibilities for the coming decade. As we gathered for our first meeting, broad optimism was tempered with caution. One contributor argued that "the present way we work will not sustain the next decade of vaccines". Another said that despite the manifest successes of today's vaccines, we had to face up to "a relative failure". We have not created a sustainable environment for new vaccines to thrive. This Series on the new decade of vaccines explores why there is an unprecedented opportunity for vaccines, but also why we must choose a different trajectory for this future decade if those opportunities are to be fully realised.

In truth, the global prospects for vaccines seem fragile. Consider recent events. In October, 2009, the UK's *Sunday Express* ran the front-page headline, "Jab 'as deadly as the cancer'". The report referred to the tragic death of a 14-year-old girl who had recently received a vaccine against cervical cancer. The link between the vaccine and her death was quickly proven to be incorrect. But sensational reporting risked inflaming public attitudes about the vaccine's safety. In January, 2010, Thai public health officials faced questions after a woman who received the H1N1 influenza vaccine suffered a miscarriage. Although experts tried to reassure women that the vaccine was safe, authorities were forced to suspend vaccination programmes pending an inquiry. And in March this year, Japanese health officials suspended vaccines against pneumonia and meningitis after the deaths of four children, despite there being no reliable evidence to substantiate public concerns. The traditional response of public health to concerns about vaccine safety is usually to give confident reassurance to the public. This approach often succeeds. But with a more sceptical and questioning media, a more responsive way forward may be, for example, to anticipate public concerns by reporting background rates of possible adverse effects so that, if they do occur, the public (and media) are neither surprised nor alarmed.[1]

The challenge faced by the global health community in creating a supportive culture for vaccines is not only one of public confidence. The systems to supply vaccines to where they are most needed—including the capacity of cold chains—are presently inadequate. In addition to logistical difficulties, vaccine production itself is unsustainable. For example, most vaccines funded by the GAVI Alliance are produced in countries outside Africa, despite sub-Saharan Africa accounting for more than half of the world's poorest countries in receipt of those vaccines. There should be stronger efforts to build infrastructure and create the skilled workforce needed to source vaccines from local producers. There are also critical ethical challenges that have so far received little public discussion. For instance, how should governments allocate limited supplies of vaccine during an epidemic?

One institution that can rightly take credit for mobilising countries and partners to create a new era of opportunity for vaccines is the GAVI Alliance. Founded in 2000, GAVI has accelerated the transfer of technologies from rich to poor countries at unprecedented rates. But GAVI's continued success is not guaranteed. It needs and deserves substantial and sustained financial replenishment. GAVI's foray into health-systems strengthening has been important and valuable (and needs to be developed still further). But it also led to anxieties that GAVI was blurring what should be its central concern—vaccines. A recent and poorly managed change in leadership at GAVI was at least partly precipitated by this feeling of mission drift. Some evidence also exists that vertical health initiatives, such as GAVI, are not without their own complications and adverse effects.[2] The way the organisation is audited is currently not fully optimal.[3] And GAVI needs to be clear about what it should not do. While evaluating its performance should be a stronger part of GAVI's remit, developing its own research agenda would, we believe,

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be a mistake.[4] Other organisations are better placed to fund and conduct vaccine-related research.

Part of the problem GAVI faces is its isolation from other initiatives dedicated to women's and children's health. Ban Ki-moon's 2010 Global Strategy for Women's and Children's Health sets out a comprehensive approach to reaching Millennium Development Goals (MDGs) 4 and 5 for the world's poorest countries. The strategy is broad, inclusive, and ambitious. It commands the support of all health agencies and donors. It has been fashioned through collaboration with countries most threatened by the diseases of poverty that affect women and children. Vaccines are a key part of the Global Strategy. GAVI is given special prominence as a means to bridge financial gaps for funding health programmes. But GAVI itself has been too silent on its contribution to the larger goals of the Global Strategy. It feels a reluctant partner. GAVI needs to position itself as a leading advocate for and contributor to that strategy. It must not be run as an institution divorced from, and without responsibilities to, this larger effort.

The Gates Foundation's notion of a Decade of Vaccines is not merely an advocacy message. It is a joint initiative between WHO, UNICEF, the US National Institute of Allergy and Infectious Diseases, and the Gates Foundation. Launched in December, 2010, it plans to increase coordination across the vaccine community and to create a global vaccine action plan. The focus of the initiative is on delivery and coverage, immunisation systems, equity, and filling the finance gap to achieve these objectives. Country consultations to be completed by the end of this year aim to build commitment to vaccines. A "prioritized delivery action plan" is to be ready by June, 2012. But substantial challenges confront efforts to scale up commitments to vaccines. Many countries have no immunisation technical advisory group to give guidance or leadership on immunisation policies. High prices of new vaccines continue to slow prospects for their delivery. Adverse media reporting can damage vaccination programmes—eg, for *Haemophilus influenzae* type b containing vaccines in several countries. And, like GAVI, in the Decade of Vaccine documents we have seen there is little or no mention of the part this initiative has to play in the Secretary-General's Global Strategy. The risk is, again, that at country level a new and highly focused vaccine initiative will compete with a broad strategy for achieving the MDGs. The two initiatives need to be linked much more closely, perhaps even integrated.

The Lancet's Series tries to trace the elements of a plan for vaccines in the 21st century. Vaccines face a strange paradox. While civil-society movements demand access to new interventions—from antiretrovirals to emergency obstetric care—there is not the same fervour about access to vaccines. The notion, expressed elsewhere in global health, of the right to the highest attainable standard of health is rarely expressed in the field of vaccines. For these attitudes to change, the vaccine community, together with its partners, has an opportunity to rewrite the terms of engagement between vaccines (as part of a larger package of services) and communities threatened with vaccine-preventable diseases. While the past has much to teach us, it is the future of vaccines that must command our priority today.

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A call to action for the new decade of vaccines

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No medical intervention has such an unambiguous track record of preventing morbidity and mortality from infectious diseases than that of vaccines.[1] The type of vaccine-preventable diseases ranges from the acute (eg, measles or meningitis) to the chronic (eg, liver and cervical cancers). Further reduction of deaths and disability from infections remains a major challenge. Few would deny that there is a moral imperative to make vaccines widely available on an equitable basis, but governments are frustratingly

slow to grasp a different and compelling argument: vaccines create wealth.[2,3]

This tenet is especially true for the poorest countries, where infectious diseases account for almost half of all deaths.[4] About 90% of these deaths are caused by six infection-related diseases: diarrhoeal and respiratory diseases of children, AIDS, tuberculosis, malaria, and measles. But encouraging progress has been made; the availability of rotavirus vaccines against one of the major causes of childhood diarrhoea has great potential.[5] Pneumonia is the leading cause of child death, and glycoconjugate vaccines against pneumococcal pneumonia—the cause of more than a third of all pneumonia deaths in infants—are now reaching children in the poorest countries.[6] A highly effective vaccine has substantially affected the burden from measles, although it does not provide protection among infants aged 4–9 months; however, research efforts towards an inhalable measles vaccine[7] might provide protection for this vulnerable group. It is also hoped that a malaria vaccine will be licensed within the next 3 years or so.

One powerful and encouraging mechanism to realise the transformative contributions of immunisation to global human health and strengthened economic development is through efficient global partnerships. The effectiveness of global partnerships has encouraging precedents. For example, an estimated 2·7 million deaths per year were attributable to smallpox in 1967, but this disease has now been eradicated.[7] Although many challenges remain, the future eradication of poliomyelitis will contribute substantially to human wellbeing and productivity, and would free up resources to be devoted to other vaccine-preventable diseases. A notably successful partnership is that of the GAVI Alliance, which has provided sufficient vaccine to save an estimated 5 million lives in developing countries.[8] This is the good news, but GAVI is compromised by a shortfall of funds to distribute vaccines for which it has made a commitment, let alone those that it has earmarked for the future. Although resources have been allocated (most recently US$100 million) to roll out a glycoconjugate vaccine against meningococcus A (MenAfriVac), at a cost of less than $0·50 per dose,[9] this is still far less than the $370 million costed to implement the vaccine in all areas where it could be effective. Clearly, to deliver improved and new vaccines, there is a funding shortfall of many billions of dollars. But there is also a need not only for alternative mechanisms of funding that are more sustainable, but perhaps also for countries to become more self-reliant so that GAVI's funds can go further.[10] Further, clinical trials of much needed improved vaccines, such as those for tuberculosis, are not moving ahead as rapidly as they should. One reason is that although improved technology has resulted in more efficient and safer vaccines,[11,12] they are more complex to investigate in the field.[13] Science has made the advances necessary for these and other important future vaccines—eg, against infections caused by *Leishmania* spp, respiratory syncytial virus, dengue, shigella, and *Salmonella enterica* serovar Typhi—to enter clinical trials, but only if substantial funding can be made available. This call to action (panel) comes at a crucial time. In some communities, recent declines in vaccine uptake provide a stark reminder that public confidence and trust in immunisations is fragile and requires attention.[14]

Our call to action for the new decade of vaccines embraces four key elements. First, we need to find the requisite funds for the research and development of about 20 improved or novel vaccines in the next decade and beyond. Most important are vaccines for tuberculosis, AIDS, and malaria, but several tropical diseases are inexcusably neglected, including leprosy, trachoma, onchocerciasis, lymphatic filariasis, leishmaniasis, and common helminthic infections such as hookworm. We must also consider vaccines beyond classic infections, such as insulin-dependent diabetes, cancers, and degenerative diseases. The world is at last taking the issue of immunisation in the poorest countries more seriously, but research is needed to adapt existing vaccines for developing-country use and to create technologies that would allow needle-free immunisation,[15] or to provide greater thermostability[16] to licensed vaccines for rotavirus and other childhood infections. We need research that will facilitate vaccine distribution through appropriate low-cost combinations and newer adjuvants—eg, those that are dose sparing or able to reduce the number of

***Panel*: Call to action for the new decade of vaccines**

Our call to action for the new decade of vaccines embraces four key elements:

- Intensified research and development, including financing and prioritising of phase 3 trials
- Advocacy at highest level to mobilise donor community
- Increased compliance and shouldering of responsibilities by developing countries
- An expanded effort in communicating benefits of vaccines, aimed at the general public, decision makers, and relevant health professionals

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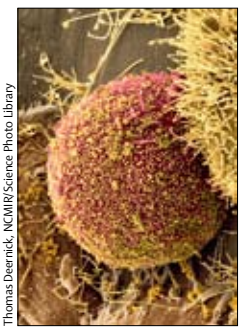
Thomas Deerinck, NCMIR/Science Photo Library

immunisation visits. A strong argument can be made too for research aimed at adaptation of regulatory frameworks to allow vaccines to be more rapidly and widely introduced without compromise to safety. Such research should particularly take into account that licensing procedures in wealthy countries are based on principles that are appropriate for populations who have low risks of serious infection and no tolerance of adverse events, but that might be inappropriate in other epidemiological settings. Research is also needed to identify biomarkers and surrogate endpoints to facilitate earlier approval of products, complemented by phase 4 post-implementation trials, to verify the links between chosen endpoints and clinical effect. For example, the US Food and Drug Administration has a programme for accelerated vaccine approval based on surrogate endpoints. But careful attention should be paid to ensure that regulatory processes do not create unnecessary, costly obstacles to vaccine development.

Second, advocacy is needed to mobilise political will for financing of vaccines. Vaccine advocacy has a distinguished record. From the leadership of UNICEF in the 1980s, to the creation of GAVI in 2000, vaccines have occupied a special position on health's political agenda. Nevertheless, advocacy initiatives have been inconsistent, leading to a loss of momentum to take advantage of the many opportunities that vaccine science will present in the next decade.

The task for advocates is difficult. Sometimes advocacy can overreach itself, as might have been the case with HIV and malaria vaccines, leading to unfulfilled hopes that can create conditions for a loss of public confidence in scientific and public health institutions and messages. In the early years of research into HIV vaccines, for example, too many international AIDS vaccine initiatives claimed that a vaccine would be available in just a few years. But the fact that an effective vaccine against AIDS still remains an elusive goal now surely casts doubt on the wisdom of these advocacy messages, even though they were well intentioned. Advocates who made claims for simplistic technological solutions may have contributed to a lack of interest and research into programmes for AIDS prevention.[17,18]

A way forward is for advocacy campaigns to draw on research evidence from related specialties to inform their strategies and messages. One specialty that might be worth comparison with vaccines is that of newborn health, in which investigation of neonatal survival has succeeded in becoming an issue commanding global interest and political commitment.[19] Four factors were crucial: stakeholder power, ideas, issue characteristics, and political contexts.

Stakeholder power means coordinated networks of individuals and groups aligned behind the initiative in question, with a clear guiding institution to lead the advocacy. For vaccines, there are many such stakeholders. Whether across the UN, civil society, the private sector, academia, or philanthropy, these networks remain disconnected with no obvious guiding body. The time-bound Decade of Vaccines collaboration—an initiative involving WHO, UNICEF, the US National Institute of Allergy and Infectious Diseases, and the Bill & Melinda Gates Foundation—could provide short-term leadership. But, as yet, there is no sustainable mechanism to bring together stakeholders in vaccine science, public health, and advocacy.

Any successful movement in global health needs a defining idea around which to mobilise. For vaccines, the idea is simple: vaccines save lives, prevent suffering, and create wealth. For example, if the GAVI Alliance was fully funded (with an additional $3·7 billion), 4 million lives could be saved between now and 2015, through immunisation programmes that reach more than 240 million children worldwide.[20] To achieve this funding, the issue must have two characteristics. First, it should represent a severe problem. Vaccine-preventable disease as a contributor to mortality in children younger than 5 years is certainly a severe public health burden. Second, that problem must be tractable: we must be able to do something about it. Vaccines provide an almost perfect example of an intervention that we know will work to prevent unnecessary deaths and economic losses.

Finally, there must be the right political context, which means that other stakeholders need to make vaccines their priority, and there needs to be a policy window to create opportunities for action. For vaccines, political stakeholders are stepping forward—notably, the Norwegian and UK Governments, which are willing to lead nations in making substantial new commitments to vaccine supply. And a window now exists, with new possibilities for financing and advocacy (the GAVI Alliance pledging conference takes place on June 13, 2011, in London; and the Decade of

Vaccines collaboration, established in December, 2010, will continue until mid-2012).

By balancing compelling but responsible advocacy for vaccines with a more strategic approach to transmitting and amplifying messages about those vaccines, the next 5 years offer prospects for unprecedented reinvigoration of public commitment to immunisation.

Third, developing countries and local communities need to increase their ownership of immunisation programmes. In view of the rich array of vaccines that have recently been licensed or are in development, donor funds alone are unlikely to meet the total cost of deploying them all. The GAVI Alliance favours copayments from affected countries, although at times these have been only small amounts. Most developing countries accord too low a priority to health in their budgets. They must be persuaded to take more of the burden themselves on behalf of their poorer citizens. Ultimately, expansion and sustainment of access to the benefits of immunisation requires ownership of the programme by developing-country governments and the communities that they serve.

Too often, immunisation programmes are driven by external forces, and national input to key decisions is either limited to a few voices or comes too late in the process. Improvement in country autonomy in decision making for vaccines requires strengthening of country institutions and their capacities, and alignment of incentives to promote autonomy in the long term, even when it might be inconsistent with achieving short-term goals. The increasing number of countries that are establishing their own vaccine policy committees (known as national immunisation technical advisory groups)[21] is an important step in building institutional capacity for local decision making, and one that will permit them to better assess and adapt or reject evidence-based policy recommendations from other national and international sources.

Increasing recognition of global health as a human right strengthens the need for increasing country ownership of their programmes. Immunisation, with its proven cost-effectiveness, would be an excellent place to begin. Many low-income countries might not be able to finance their entire immunisation programme fully in the short term from domestic sources. However, many of these countries can finance more than they now do and take steps to make their small domestic financing commitments more stable. For example, addition of a line item for immunisations to the national budget is a policy action that would make immunisation funding more predictable and stable than it is at present.

Equally importantly, many low-income countries are now becoming lower-middle-income countries with more national budget available to them. In these transitions, health budgets must increase to reasonable amounts, with a commensurate increase in domestic financing for their immunisation programmes. Through the building of institutional capacities for decision making, a concerted effort to turn political will into supportive legislation, and economic growth, developing countries are poised to take an increasing ownership of their immunisation programmes over the next 10 years.

Fourth, the benefits of vaccines must be measured and communicated. Establishment of effective communication that bolsters advocacy and sets up a solid platform for trust and confidence in vaccines is a challenge.[5] The global scenario of immunisation in the next decade is changing and dynamic, as a result of the interplay of several factors. Among these factors, we can identify that the underpinning science and technology have resulted in much safer vaccines and more effective protective immunity. But improved safety and effectiveness also mean higher production costs and more complex vaccines. Further, improved delivery of vaccines has been achieved through combination of antigens that can be delivered in one, not several, injections, but which are complex formulations. Immunisation programmes are already, and will be increasingly, tailored to reflect differences in epidemiology, disease priorities, and targeting of different age-groups—eg, elderly people. Consideration of the genetically determined susceptibility profiles of individuals to disease and adverse reactions will further complicate the issue. Many of the most important diseases for which we do not yet have licensed vaccines will make unprecedented demands on our scientific ingenuity and a greater imperative to communicate these sophisticated concepts to governments, health professionals, and the public.

The challenge is that between development of a vaccine and its public consummation there is a so-called black box within which a multiplicity and heterogeneity of human factors must be negotiated to realise the public

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health gains of immunisation. If trust and confidence in vaccines is not secure, our efforts to advocate increased resources to make possible the necessary research, development, and supporting clinical investigation will be a bridge too far. Clearly we do not have answers to many basic questions. What is needed? What motivates people to be immunised? What deters them? Undoubtedly, fundamental questions such as these need to be given more prominence. We need to listen more. However, we have the knowledge base, expertise, and methodology with which to investigate what needs to be done to increase public trust and confidence in immunisation. We must not hesitate to use the skills and innovations of those who have a track record of success in communication—eg, in marketing consumer products or boosting television audiences. As with these examples, when sales and viewing rates measure success or failure, there is a tractable arbiter with which to test whether or not new communication strategies work because we have excellent measurements of immunisation uptake. There is a way forward and we need to grasp the opportunity.

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Will the Decade of Vaccines mean business as usual?

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In 2011, the story of immunisation coverage worldwide hovers between the glass half empty and the glass half full. Anticipated advances in vaccinology during this new Decade of Vaccines will only translate into reductions in global morbidity and mortality from targeted illnesses if fundamental restructuring means that the most marginalised countries (particularly in Africa and southeast Asia) gain access to new and established vaccines. Routine vaccine coverage and the introduction of new vaccines have increased enormously in the past 10 years, with 14·6 million more children receiving the routine diphtheria, tetanus, and pertussis vaccine in 2009

than in 2000.[1] Yet 23 million children younger than 1 year are still missed,[1] particularly those living in the poorest quintile of low-income countries who have not received the primary series of childhood vaccines.[2]

At the World Economic Forum in Davos, Switzerland, in January, 2010, the Bill & Melinda Gates Foundation launched the Decade of Vaccines by pledging US$10 billion to support worldwide efforts to develop and deliver vaccines to the world's poorest children in the next decade.[3] Although this pledge could save the lives of more than 8 million children, this sum will still not reach the potential of vaccines to contribute to the achievement of Millennium Development Goal (MDG) 4—reduce the mortality rate in children younger than 5 years by two-thirds between 1990 and 2015. Partners in the Decade of Vaccines (WHO, UNICEF, the Gates Foundation, and the US National Institute of Allergy and Infectious Diseases) know that there are crucial gaps in policy, resources, advocacy, and research that will need to be addressed if the next 10 years is really to be business unusual for immunisation access.

Although many vaccine strategies target adolescents, adults, and elderly people, the main focus of coverage remains on children younger than 5 years. In 2008, of the nearly 8·8 million deaths in children younger than 5 years worldwide, 68% were caused by infectious diseases, 18% by pneumonia, 15% by diarrhoea, and 8% by malaria.[4] Nearly half of these deaths were in five populous countries: India, Nigeria, Democratic Republic of the Congo, Pakistan, and China.[2] Many of the deaths due to infectious disease can be prevented by the introduction of new and established vaccines, while others, including malaria, tuberculosis, HIV infection, and neglected parasitic diseases, still await the development of effective vaccines. The lag in introduction of life-saving vaccines in low-income countries with high disease burden has been most tragically shown by the *Haemophilus influenzae* type b conjugate vaccine (HibCV).[5] Introduction of this vaccine in low-income countries, where most of the 371 000 yearly deaths from *H influenzae* type b occurred,[6] was started only 12 years after its institution in developed countries. It took another decade before at least 60% of children in low-income countries gained access to the vaccine.[5] This delay in HibCV implementation in low-income countries led to 6 million deaths since the vaccine became available to children in developed countries. Although lessons have been learnt from this experience, history could be repeated with other life-saving vaccines, including pneumococcal conjugate and rotavirus vaccines.

826 000 children younger than 5 years die from pneumococcal disease every year—almost three times the yearly deaths due to *H influenzae* type b.[7] However, few low-income countries have successfully enabled access to pneumococcal conjugate vaccine for children a decade after its introduction in developed countries.[5] Although uptake of pneumococcal conjugate vaccine immunisation in children from low-income countries is expected to match that in developed countries in the next 5 years, this is unlikely to materialise without the establishment of strong-willed partnerships between governments, developmental aid agencies, and drug companies. Similarly, introduction of vaccine against rotavirus, which is associated with 527 000 childhood deaths every year mainly in low-income countries,[8] needs urgent introduction into low-income countries. The GAVI Alliance is committed to promoting early access to new vaccines in 56 of the world's poorest countries. The GAVI Alliance estimates that the pattern of delay in introduction of new vaccines has meant that, for the 2008 birth cohort, many of the world's poorest children remain unvaccinated, with rates for unvaccination of 34% for hepatitis B, 71% for *H influenzae* type b, 92% for rotavirus, and 93% for pneumococcal conjugate vaccines.[1]

Vaccines are now the largest cost-driver of immunisation programmes, and this expense is probably the greatest impediment for introduction of new vaccines in low-income and middle-income countries. The increasingly complex research and technology needed for vaccine development means that new vaccines could cost substantially more to develop than the familiar US$0·50 of established vaccines. With this cost, and the increased costs incurred with expanded logistics of immunisation programmes, the biggest question for access to vaccines in poor settings is a financial one. Because more poor people live in low-income and middle-income countries than in countries eligible for support from the GAVI Alliance, how will overstretched national budgets cope with the costs of vaccine delivery without support from external donors? The GAVI Alliance has a $3·7 billion shortfall, so sustainable funding for global access to vaccines is one of the world's biggest challenges.[9] However, lessons can be learnt from existing procurement practices. First is the pooling

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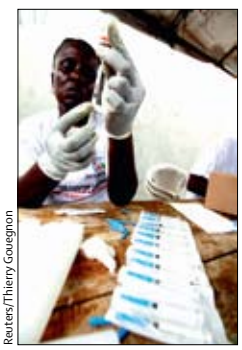
Reuters/Thierry Gouegnon

of vaccine procurement for small and low-income and middle-income countries—a system that has already been effective in lowering vaccine costs in the Americas by the Pan American Health Organization. Second, at the start of new vaccine development and introduction, a tiered pricing arrangement should be negotiated in which vaccine costs are prorated dependent on the wealth of countries. This system will enable companies to recoup research and development investments and to be profitable, whilst simultaneously minimising suffering and death in the most vulnerable individuals worldwide. Negotiations of regimes for tiered pricing are usually done with an air of secrecy and often on a country by country basis, yet the question should be asked whether mystery and market forces should continue to drive this process? Or should global public health be more transparent to ensure vaccine access and affordable pricing. But history shows that, if a few manufacturers have a market monopoly, there might be little incentive to lower prices. With increases in technology transfer to emerging vaccine manufacturers in the developing world, the security of global vaccine supplies could be increased and prices reduced by the encouragement of several suppliers for each product. All these mechanisms rely on governments being committed to strengthening their immunisation programmes.

Global and grassroots advocacy premised on robust regional data for disease burden is needed to persuade politicians about the importance of vaccines as a public health tool, and to show this commitment with a budget line-item for immunisation services. Part of this advocacy should be the establishment of strong national immunisation technical advisory groups whose mandate is to advise about national policies for immunisation practices. For countries with limited human resources, constituting authoritative advisory groups has been difficult, and, in these settings, regional committees should offer immunisation advice to countries.[10] Vaccination of children needs reductions in vaccine costs, but countries should also address why so many children remain inadequately vaccinated. Vaccine hesitancy as an indication of gaps in parental knowledge or refusal to allow immunisation is an increasing concern worldwide. A systematic review of children who are undervaccinated identified the reasons for undervaccination as insufficiencies in the immunisation system (44% of children), parental attitudes and knowledge (28%), family characteristics (21%), and communication and information (7%).[11] The failure of the immunisation system was characterised by issues that are familiar to many struggling public health systems in the developing world, including distance to services, missed opportunities (ie, children not being vaccinated when they are seen at health centres), low knowledge among health workers, and unavailability of vaccines. Introduction of the best technology into failing health systems will have suboptimum impact.

Vaccine services have traditionally been run as vertical stand-alone programmes, and efforts for poliomyelitis eradication are encouraging these services to focus even more single-mindedly on eliminating one disease. Furthermore, there are demands for vaccination services to become closely integrated within comprehensive primary-care services, so that missed opportunities for vaccination are reduced, and immunisation services can be used as a springboard for other interventions. The bottom line for many poor countries is that public health services are struggling to deliver good-quality services across the board, and, to achieve the MDGs, the strengthening of health services probably needs the most attention.

The challenge of ensuring progress in those who stand to gain most from advances in vaccinology over the next decade needs a sea change in the way that vaccine advocacy is considered. If lessons are taken from HIV activism, it was international grassroots pressure that created the demand for global access to antiretroviral drugs. Why then can a social movement not be created in support of vaccines? Admittedly, the appeal of vaccine-preventable diseases is different. In the developed world, because the diseases have largely been eliminated or greatly reduced, children are being immunised against an unseen threat. In the developing world, death from common childhood illnesses is commonplace and is regarded as part of the condition of poverty. Perhaps the voice of poor nations can be mobilised to demand vaccines as part of a broader call for global health equity. The 2009 experiences with the H1N1 influenza vaccine showed that, in a threatening pandemic, the developed world had access to vaccines but poor countries received too few vaccines that arrived too late to have made an impact should the pandemic have evolved. These experiences lead to the final

question about who is responsible for global decision making for vaccine policy, strategy, and financing.

Although WHO is the main global health structure with international legitimacy, it has been criticised for a reluctance to influence crucial global health issues. The nature of vaccine-preventable diseases makes immunisation both an important global health issue and a matter of equity; therefore, immunisation must be a priority for action and financing by WHO. However, one agency alone cannot influence the complexities of immunisation. There must be dialogue with various stakeholders, including civil society, governments, the private sector, and donor agencies. Only with this dialogue could the partnership envisaged in the Decade of Vaccines become a powerful force seeking newer and bolder actions than before, in the knowledge that the value of a life is equal worldwide.

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Is immunisation child protection?

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The Lancet's Series entitled new decade of vaccines shows the great opportunities for, and many challenges that face, successful development and implementation of vaccines in the coming decades. The Series emphasises recent advances in biomedical sciences, particularly molecular microbiology, immunology, and genetics. But the biggest hurdle to realisation of this potential could instead relate to failure of parental acceptance of safe and effective vaccination.

Refusal of parents to vaccinate their children is an example of the conflict between the best interests of children and the autonomy and interests of parents. It raises the issue of the extent to which state authority can interfere in private family life to protect children. This conflict can be approached from different ethical perspectives and theories.[1] However, the basic underlying principle is that children's interests need to be protected.[2] Historically, children were viewed as the property of their parents, but they are now recognised as vulnerable and dependent individuals who are in need of protection through instruments such as children's rights.

Liberal democracies are characterised by neutrality to different conceptions of the good life, or citizens' own interests. That is, every adult enjoys freedom to form and act on their own conception of what is best for their life. This freedom spills over into parenting, in which parents are afforded considerable freedom to rear their children according to their own values and conception of best


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interests. But, unlike adults, the freedom of young children is highly restricted because they are not competent and cannot autonomously accept risks to which they are exposed. Children should not be exposed to clear, direct, and substantial risks of harm. Thus parents are not ethically or legally permitted to refuse life-saving blood transfusions or medical procedures on the basis of their conception of what is best for their child.[2] Any deviation from a widely accepted account of the interests of a child must be reasonable. High risk of death or serious illness is not reasonably in a child's interests.

Notwithstanding important practical and ethical differences, some parallels can be drawn between immunisation and child protection. The first relates to communication. Child abuse and many vaccine-preventable infections are prevalent but are largely invisible or, at least, not widely known about. Hand in hand with this unawareness, there is a fundamental and widespread lack of understanding of these two areas of child welfare and their complexities. A consequence is that public opinion and related media communication in both areas tend to be dangerously polarised. In child protection, one hears about either disastrous failures of detection or allegedly false accusations of innocent parents or carers, both of which are very rare exceptions even assuming such reports are accurate. For vaccines, one hears unqualified celebrations of promise or success, or unfounded or anecdotal scare stories.

Emerging pressure groups and networks of highly motivated individuals—whose engagement and qualification to comment is often solely based on personal experiences and related grievances—can have a major influence on public commentary and even policy. Such groups have successfully captured the agenda on child protection through the media, the UK's General Medical Council,[3] the courts, and employers of health professionals through complaints procedures. Similarly, antivaccine campaigners have achieved prominence and influence in the media and political debate.[4] Although mainstream trends promoting public consultation and professional accountability give some legitimacy to such individuals and groups, such public debate can become distorted and harmful to the interests of children. In particular, the fundamental difference between selective assembly of evidence in support of a firmly held belief, and construction of a hypothesis that is tested through experiment and systematic observation, is often overlooked and widely misunderstood by both the public and commentators.

The second parallel relates to the role of parents in protection of their children's health and welfare. In general, society rightly entrusts the welfare of children—the future society—to parents, who have to bear the burden of care for bringing up children. Usually, parents are highly motivated to protect their children's welfare and maximise their opportunities, and can be relied on to make sensible decisions. Moreover, they have privileged access to their child's circumstances, social networks, and living conditions. But as vulnerable and dependent individuals, children's rights have to be protected ultimately by the state in its *parens patriae* role. In some situations, the best interests of the child diverge from the views and actions of the parents, unless an extreme version of ethical relativism is accepted. In the case of a violent or neglectful parent, well defined mechanisms are in place to protect the child. But should the same principle pertain to parents who refuse immunisation and thereby fail to take the necessary action to protect their children from preventable and potentially serious infection? Does the failure to immunise a child against a serious infection with a safe vaccine constitute child abuse? Should the state intervene to ensure children are protected from serious infectious diseases?

The analogy with child abuse is clear when the imminent risk to the child is high without intervention—eg, a child bitten by a rabid dog or a newborn baby of a woman infected with hepatitis B.[5] In such cases, the health-care profession has a very strong case to ask a court to mandate intervention when parents refuse immunisation. However, the analogy becomes complicated for most common childhood infectious diseases, such as measles, diphtheria, and pertussis. Protection from infections is something children should reasonably be able to expect as a general right. However, in countries where particular infections are rare—often because of widespread immunisation—the actual risk of remaining unimmunised might be quite small or even non-existent. In this situation, parents expose their children to a very small risk by refusing vaccination. The situation can even arise—as it did with oral poliovirus immunisation in the UK for a period before 2006—in which the risks of immunisation, although extremely small, exceed those of refusing the vaccine, provided that only a few individuals remain unimmunised.[6] Generally,

immunisation not only protects the health of the child, but also contributes to protection of all children. When enough parents opt out from immunisation of their children, infections increase in unimmunised or otherwise unprotected individuals, as is occurring with measles throughout western Europe.[7]

In this situation, the social contract between the state and the parent, on behalf of the child, is also a contract about the common good. Although an abusing parent should obviously be prevented from harming or neglecting their child, the ethical argument to require a parent to have their child immunised in the context of high herd protection is weaker and less clear. It has an element of altruism and beneficence. Paradoxically, as more parents refuse, compulsion to immunise becomes easier because the risk to individual children rises. Thus, in cases of low herd protection, the state has a compelling reason to require immunisation with safe vaccination against serious infectious illness because the risks to children of being unvaccinated are substantially increased. In this case, immunisation is a matter of child protection and the state has to secure the interests of children. An example could be a highly virulent pandemic strain of influenza. However, events of the H1N1 influenza pandemic in 2009 suggest that the threat of even moderately virulent influenza quickly induces widespread demands for vaccination, indicating that the evident threat of serious disease makes compulsion unnecessary.

The third parallel relates to the need for protection of unvaccinated children in an epidemic in which demand for vaccination is insufficient, despite the fact that vaccination is safe. Parents are not legally entitled to refuse medical treatments which are substantially in their child's best interests.[2] For example, Jehovah's Witnesses cannot refuse life-saving blood transfusions on their child's behalf on the basis of their own religious beliefs, even though they can legally refuse them for themselves.[8,9] In such cases, the court exercises a *parens patriae* role and authorises treatment for the child. During epidemics in which vaccination is the most effective way to protect a child, the principle that parents should be prevented from refusing clearly beneficial treatment for their children could be extended to prevent parents from refusing adequate protection for their child. Such cases are extreme and, generally, the issue of vaccination is best managed without compulsion but rather through good communication of accurate information. Liberty should be restricted, in a liberal society, only when there is a clear and direct threat of harm to innocent parties who cannot respond for themselves. Less coercive interventions should be exhausted before more coercive measures are used. This principle—that vaccination should not be compulsory unless risk is high and vaccine acceptance is low—is gaining support.[1,10]


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Faced with the sometimes conflicting values of parental liberty and the need to protect children from infectious disease, where should we turn for guidance? Perhaps to parents. Again the comparison with child protection is instructive. In child protection, the number of parents who adequately care for their children is irrelevant to a child at risk. However, for infectious diseases transmitted between human beings, the more parents who protect their children through vaccination, the higher the herd protection and the lower the risk for any non-immune children. Of the many parents who have their children fully and promptly immunised, the proportion who are fully aware of the broad benefits of immunisation is not precisely known. However, most parents actively support childhood immunisation, and when the opportunity arises to participate in clinical trials, which are essential for the development and licensure of new vaccines for children, there are always parents prepared to volunteer their children to participate once full information has been provided. Therefore the kind of parental altruism that society needs to make such public health programmes work and survive does exist. The challenge remains to harness this goodwill to protect all children.

Just as we owe it to our children and their children not to destroy the environment in which they will live, we also owe it to them to pass on an environment in which they can be unexposed to the entirely avoidable risks of many infectious diseases. The moral imperative is clear and the question is not whether to do it, but how. For immunisation, unlike child protection, vaccination of enough individuals can lead to protection for all. This is a unique opportunity to work together for the common good.

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Public–private collaboration in vaccine research

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Public sector scientists, for example those based in universities or in public health institutes, often collaborate with commercial organisations—including vaccine manufacturers—while taking on various advisory roles, mainly to regulatory agencies and policy makers.[1] To what extent do these many roles constitute unacceptable bias or compromise? At one extreme, scientific independence of an individual or organisation might be inevitably compromised by commercial collaboration,[2] whereas a contrary perspective argues that to systematically uncouple public health organisations from links to industry would deny or compromise the provision of crucial advocacy.[3] Research and expertise in relation to immunisation policy decisions deserve special attention, because they affect the future health of large numbers of individuals. We believe that the public–private interface in vaccine research should be preserved.

***Panel:* Suggested criteria for vaccine research projects when public health institutes consider partnership with private industry**

- Public health impact of vaccine could be substantial
- Expertise inside institute is appropriate to the task (and, preferably, institute is better placed to take the project than other alternatives)
- Project competes well in internal prioritisation of use of resources inside institute
- Intellectual property issues and ownership of data can be agreed on
- All scientific results can be published without censorship
- Funds for infrastructure and basic functions of institute do not depend on research contracts with industry

The research, development, and implementation of a vaccine are complex and costly processes. Provision of vaccines is a necessarily public–private partnership because, with few exceptions, only commercial vaccine companies have found it feasible to follow through on the difficult and expensive responsibility of development of a high-quality, safe, and effective product. However, the public sector is the only sensible and practical source of much of the epidemiological, microbiological, and immunological data that are essential to the development and implementation of a vaccine. Furthermore, outsourcing of clinical trials to established and approved research organisations, in accordance with strict regulatory guidelines, is an essential step in the registration of any new vaccine.

Two articles in *The Lancet*'s Vaccine Series describe some of these scientific challenges from the perspective of the vaccine industry.[4,5] Private companies are in a position to provide essential information for judicious immunisation policies, but the primary responsibility for protection of the interests of the public lies in the public sector. In the past, fruitful collaboration has resulted in the development of vaccines with significant public health benefit.

The US National Institutes of Health and its Vaccine Treatment and Evaluation Units played a crucial part in early development of several important vaccines:[6,7] eg, *Haemophilus influenzae* type b conjugates, hepatitis A, rotavirus, and human papillomavirus vaccines. In Canada, many vaccine-related organisations and universities were essential for the development of an acellular pertussis vaccine, research

and development of vaccine adjuvants, and assessment of vaccines for immunisation programmes.[8] The UK Health Protection Agency lists vaccine development and evaluation as one of the science themes essential for the evidence-based protection of the health of the population.[9] The UK's Department of Health and Health Protection Agency contributed substantially to the evaluation, licensure, and rapid implementation of meningococcal conjugate vaccines in the UK during meningococcal epidemics in the country. Our own institute, the National Institute for Health and Welfare in Finland, has contributed to the advanced phases of clinical development and to postlicensure research of *H influenzae* type b and pneumococcal conjugate vaccines. Thus the interdependence of public and private sectors is an indisputable and crucial component in the provision of safe and effective vaccines, and will probably remain so indefinitely.

Management, rather than disruption, of the public–private partnerships that underpin the provision of immunisation programmes is crucial.[10] Measures that could be used to minimise the potentially harmful effects of conflicts of interest are: comprehensive and structured disclosure of potential conflicts of interest (including non-financial conflicts, such as expert testimony, membership of a governmental or other advisory board, relation with lobbying or advocacy organisations, charities, or funding bodies); interposition of an intermediary between donor and recipient in any financial relation; surveillance for fraud; transparency of the expert recommendation process; and provision of training to raise awareness of different forms of bias, accompanied by practical measures to limit exposure to marketing activities. In addition to management of interests, public health institutes need solid criteria for projects that can be undertaken in conjunction with industry (panel).

Postlicensure safety surveillance of new vaccines that are widely used in immunisation programmes is crucial to both regulatory and public health authorities, and to vaccine manufacturers. This activity should be paid for, but preferably not supervised and conducted by, the marketing authorisation holder. The marketing authorisation holder should be obligated to pay a specific surveillance fee to an independent body (eg, the European Medicines Agency, the European Centre for Disease Prevention and Control, or a non-governmental foundation) at the time of licensure. This body would then allocate funds to public research organisations that would actually undertake safety and effectiveness surveillance of the vaccines.

Vaccine companies need partnerships with the public sector to develop new vaccines that benefit public health. The involvement of the public sector in vaccine research not only directs development towards public health goals, but also ensures that research seeks to answer questions relevant to public health decision makers. Vaccine research and development benefits from maximum transparency, clear rules, and exchange of critical views on the research itself, rather than from discussion about the qualities and relations of the researchers. Thereby the public good is fostered, not jeopardised.

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The last mile in global poliomyelitis eradication

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Before the development of the inactivated poliovirus vaccine (IPV) in 1955, poliomyelitis paralysed and killed up to half a million people every year. The introduction of the IPV in the USA led to a dramatic reduction in poliomyelitis transmission and cases, from an average 20 000 cases per year in the 1950s to less than 1000 cases by the 1960s.[1] With the development of the oral poliovirus vaccine (OPV) and the strategy to give two doses of trivalent OPV to all children younger than 5 years in mass vaccination campaigns, transmission was stopped in the USA by 1979.[2] Similar campaigns were launched in many developing countries, notably in Latin America, following an initiative by the Pan American Health Organization to eradicate poliomyelitis in the Americas by 1990. In 1988, the World Health Assembly (WHA), with support and funding from Rotary International, unanimously launched a global goal to eradicate poliomyelitis by 2000.[3] Since then the achievements of the Global Poliomyelitis Eradication Initiative, one of the largest global public health programmes, have been remarkable. From a situation in which poliomyelitis was endemic in 125 countries on five continents, paralysing 350 000 children annually, there has been a 99% decrease in the global incidence of the disease,[4] with only 20 countries with endemic disease in 2000. One of the three serotypes of wild poliovirus (serotype 2) has been eradicated since 1999.

Despite these impressive initial gains, the last phase of poliomyelitis eradication has been difficult, with uneven progress over the past 5 years (figure). In recognising these trends, WHA called for a new plan to complete the eradication effort and the global eradication strategy was revitalised at its 61st session in May, 2008. Over the past 2 years, transmission of indigenous wild poliovirus types 1 and 3 has continued in geographically limited areas in four countries (Nigeria, India, Pakistan, and Afghanistan), and has also affected countries with low coverage of routine immunisation and weak health systems in central Africa and the horn of Africa.[6] Nigeria and India have made enormous gains in the control of poliomyelitis throughout the past year with a more than 90% reduction in cases. Even war-torn Afghanistan has shown a 34% reduction in cases, but Pakistan remains a huge challenge. Inefficiencies within the eradication programme in Pakistan, compounded by recent floods and a smouldering conflict in the north, were associated with a 62% increase in cases, with 144 confirmed children with poliomyelitis in 2010 and over 35 cases in the first quarter of 2011.[7] In view of these concerns about slow progress in global eradication, WHO's Director-General established an Independent Monitoring Board of the Global Poliomyelitis Eradication Initiative in 2010. The Board's most recent report (April, 2011)[5] presented a mixed picture, noting impressive gains in some parts of the world and residual challenges in others. The overarching theme of the Board and global public health community is continued emphasis on implementation and close monitoring of the current eradication strategy.

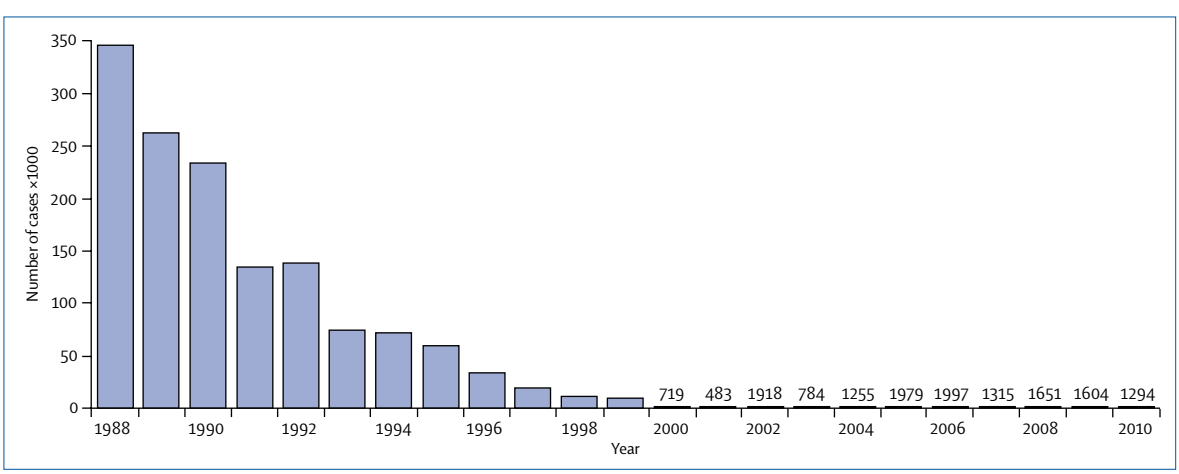
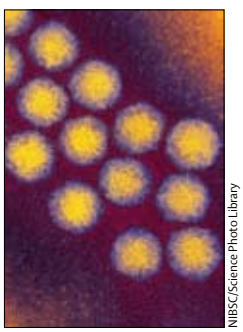


Figure: **Global trends in number of cases of poliomyelitis**
Adapted from Independent Monitoring Board of the Global Polio Eradication Initiative.[5]

The Board has rightly underscored several crucial success factors, such as political support, vaccine efficiency, sound surveillance strategies, operational innovations, and demand creation. However, there is a funding gap of US$665 million from the $1·21 billion required for 2010–12.

Notwithstanding the importance of continued focus on staying the course, there are other crucial but neglected issues. Remarkably little public debate about these issues has taken place nationally or globally. Broadly, the issues can be summarised as three challenges which must be met if poliomyelitis is to be eradicated. First, there is a knowledge gap that must be confronted and addressed. Despite the remarkable success of the OPV over time, the current product might not be ideal for the last phase of eradication and for clearing residual pockets of disease. Although impressive seroconversion rates have been reported from many parts of the world,[8,9] the trivalent or monovalent vaccines are not uniformly effective. Of the 144 patients with confirmed poliomyelitis in Pakistan in 2010, 43% had received four or more doses of OPV, suggesting that the vaccine might not be effective in a subset of the population.[10] Poor seroconversion after vaccine administration in undernourished children has been reported (Petri W, University of Virginia, VA, USA, personal communication; and my own observations). Although the research needed to develop more effective vaccines and vaccination strategies should not detract from the current global initiative, we need a greater understanding of the vaccine's effectiveness, or lack thereof, in population subsets.

Mucosal immunity induced by the current OPV is imperfect and potentially allows immunised individuals to participate in asymptomatic wild-type poliovirus transmission in settings with efficient faecal-oral transmission of infection. 0·74% of fully vaccinated and asymptomatic children in India continued to excrete wild poliovirus types 1 and 3, and two-thirds of these children had received six or more OPV doses, which is a concern.[11] The most recent outbreak of infection, involving 315 cases of type-2 circulating vaccine-derived poliovirus (cVDPV2, >1% divergent from Sabin 2) occurred in Nigeria between July, 2005 and June, 2010, when 23 of 34 supplementary immunisation campaigns used monovalent or bivalent OPV lacking Sabin 2.[12] The increased use of serotypes 1 and 3 monovalent OPV might have resulted in improvements in vaccine-induced population immunity against these serotypes, and in declines in immunity to cVDPV2.[13] These findings are indicative of the need for control scenarios to take into account the possibility of dealing with virulent vaccine-derived polioviruses at scale, and the potential benefit of including IPV in the eradication strategy in such countries.[14] The successful development and use of bivalent OPV is a welcome step for improvement of eradication strategies,[15] as are trials of fractionated doses of IPV[16] which could make the product more affordable, either singly or in combination with OPV.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Second, are the current strategies for eradication satisfactory? The usual approaches to eradication for the remaining pockets of endemic disease are large-scale national and subnational immunisation days. The evolving epidemiology of poliomyelitis also suggests that population immunity-thresholds needed to interrupt wild-poliovirus transmission differ around the world, and are substantially higher in northern India and parts of Pakistan than in Africa and elsewhere. Although this understanding has led to the systematic development of targeted district-specific and population-specific strategies, and capacity to address heterogeneity in OPV coverage, the mainstay is still a largely vertical strategy for eradication, often distinct from routine expanded programmes for immunisation services. Whereas this separation has not been an issue in countries with strong programmes, in countries where these services are dysfunctional, serious issues of vaccination-programme mismatch are created, affecting overall control.[17] For example, of the 144 patients with poliomyelitis in Pakistan in 2010, 67% were younger than 2 years and 68% had not received any routine immunisation.[10] This finding is indicative of the difficulty of trying to eradicate poliomyelitis through a parallel programme delinked from routine expanded services. This approach is possible, but is fraught with the risk of failure. Integration of eradication strategies and routine immunisation services should be possible, because the inequity of resources, manpower, and surveillance systems for both programmes is a serious limitation for control and eradication of the disease. The risk of reintroduction of poliomyelitis into countries now free from the disease is compounded by poor overall immunisation rates, as in parts of Africa, Pakistan, and Tajikistan. Programme managers vehemently deny the lack of integration between poliomyelitis and expanded

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programmes for immunisation, but the reality on the ground suggests otherwise. Huge differentials exist between the two programmes for overall support services, financial resources, staff incentives for performance, and surveillance methods. WHO's recent decision to separate the poliomyelitis programme from the mainstream vaccination cluster also sends the wrong message when there is much need to focus on integration rather than fragmentation.

Finally, community engagement and creation of grass-roots support for poliomyelitis eradication is key, and related to the issues already mentioned. Without adequate demand-creation, and understanding barriers and addressing them systematically, approaching populations in the same way as before is naive. In many parts of urban and rural Pakistan (and possibly elsewhere), the only vaccination service that people are aware of and access is the poliomyelitis programme; and with home delivery of OPV, incentivising people to seek routine immunisations in expanded programmes is a challenge. The recognition that a substantial proportion of residual disease (both from wild viruses and cVDPV) is in children who have received multiple doses of OPV is a source of disquiet from communities. In these circumstances innovative strategies that couple OPV and IPV could be a way forward.

All these issues should not detract from the importance of staying on track in the final phase of the global strategy for poliomyelitis eradication. However, without adequately addressing some of the real barriers to eradication and creation of innovative solutions to tackle emerging issues, the risk of failure is high. Although we agree with the sentiments of Stephen Cochi, from the US Centers for Disease Control and Prevention, that "to stop now would be snatching defeat from the jaws of victory,"[18] victory is by no means assured. All resources and collective wisdom should be combined to ensure that the last mile in the race to eradicate poliomyelitis is the very last mile that we ever run in the quest to relegate poliomyelitis to the corridors of history.

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My institution has grants from WHO to measure poliomyelitis seroprevalence in Pakistan and to assess nutrition interventions and poliomyelitis response. I am also a member of WHO's Strategic Advisory Committee for Vaccines, and the Regional Techincal Advisory Group for Polio for WHO Regional Office for the Eastern Medditerranean. The views in this Comment are my own.

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New Decade of Vaccines 1

The next decade of vaccines: societal and scientific challenges

E Richard Moxon, Claire-Anne Siegrist

Vaccines against microbial diseases have improved the health of millions of people. In the next decade and beyond, many conceptual and technological scientific advances offer extraordinary opportunities to expand the portfolio of immunisations against viral and bacterial diseases and to pioneer the first vaccines against human parasitic and fungal diseases. Scientists in the public and private sectors are motivated as never before to bring about these innovations in immunisation. Many societal factors threaten to compromise realisation of the public health gains that immunisation can achieve in the next decade and beyond—understanding these factors is imperative. Vaccines are typically given to healthy individuals and safety issues loom high on the list of public concerns. The public needs to regain confidence in immunisation and trust the organisations responsible for the research, development, and implementation of vaccines. In the past, by use of a judicious amalgam of knowledge and empiricism, successful vaccines were largely developed by microbiologists who identified antigens that induced immune responses to conserved pathogen components. In the future, vaccines need to be developed against deadly diseases for which this strategy is often not feasible because of the extensive antigenic variability of relevant pathogens. High microbial diversity means that immunity after natural infection is often ineffective for prevention of disease on subsequent exposure, for example in HIV infection and malaria. Additionally, vaccines need to be generated to protect the people who are most vulnerable because of age or underlying diseases. Thus, in the future, a much deeper understanding of the immunological challenges—including the diversifying role of host genetics and environmental factors, leading perhaps to more personalised approaches—will be the touchstone for rational design and development of adjuvants that result in novel safe and effective vaccines.

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

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Introduction

This Series aims to review the potential contributions of immunisation to improvement of global health, with special attention to identification of the major scientific and societal challenges for development and implementation of safe and effective vaccines in the next decade and beyond. In the past century, the judicious use of vaccines against microbial diseases has improved the health of millions of people. Vaccines have eliminated or substantively diminished the toll of major scourges, including smallpox, poliomyelitis, measles, pertussis, tetanus, yellow fever, and diphtheria. In the past two decades, great progress has been made in prevention of meningitis, pneumonia, and hepatitis. Furthermore, an amalgam of new technologies encompassing genetics, structural biology, and biochemistry are enabling the classical disciplines of epidemiology, microbiology, and immunology to expand the portfolio of vaccines against respiratory infections and diarrhoeal diseases. Scientists in the public and private sectors are motivated as never before to bring about incisive advances through the development of new and improved vaccines in the next decade and beyond.

The spectacular past achievements and the exciting prospects for development and implementation of improved and new vaccines should be tempered by a realistic appraisal of the many challenges now and in the long term. Notably, in the past, many successful vaccines were based on induction of immunity to conserved target antigens of microbes. By contrast, many of the most

Key messages

- Vaccines against microbial diseases have already improved the health of millions of people but, in the next decade and beyond, there are extraordinary opportunities to expand the portfolio of immunisations against viral and bacterial diseases and to pioneer the first vaccines against human parasitic and fungal diseases
- In the past, successful vaccines were largely developed by identification of antigens that induced immune responses to conserved pathogen components, whereas, in the future, a major challenge is to develop vaccines against deadly diseases in which the target antigens have extensive antigenic variability
- Development of successful vaccines against pathogens with extensive antigenic diversity requires an in-depth knowledge of their molecular epidemiology, and evolutionary and population biology
- Although science is the key to development of improved and novel vaccines, it is not sufficient; the next decade demands that we also build public trust and confidence in immunisation through effective communication with policy makers and the public
- To increase vaccine safety, use of subunit antigens has been increasing, but these antigens are devoid of the natural adjuvant properties typical of whole-cell vaccines, and, therefore, are less immunogenic, and need novel strategies to increase immunogenicity
- Identification of the molecules and signalling mechanisms through which antigen presenting cells elicit specific and effective T cells is crucial for development of effective vaccines
- A major challenge is how to develop vaccines capable of conferring lifelong protection without the need for repeated booster immunisations
- Research is needed to address the particular challenges of immunisation of very young people, elderly people, and people with chronic diseases
- Increasing knowledge of the individual variations in immune responsiveness will provide a rational basis to question the appropriateness of mass immunisation and to replace mass immunisation with personalised strategies

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important diseases for which future vaccines are urgently needed are caused by viruses, bacteria, or parasites that are characterised by extreme variability of their surface structures.[1] Microbes displaying extensive antigenic diversity, such as HIV and *Plasmodium* spp, are particularly challenging; immunity after natural infection is often ineffective in prevention of disease on subsequent exposure. To induce comprehensive and durable protection to these microbes, understanding of immune responses will need to be much more detailed than at present, and vaccine formulations will need to include many different, judiciously selected antigens.

Antigenic diversity of pathogens has major implications for how science, through the public and private sectors, can identify the relevant vaccine antigens and formulate them into safe and effective vaccines. These issues are addressed, especially from an industry perspective, in the second[2] and third[3] papers in this Series. Estimates of annual total sales of vaccines projected for 2020 are in excess of US$30 billion compared with $6 billion in 2000; industry investment in research and development is estimated to be 15% of these figures, respectively.[4] The global agenda has been galvanised through, inter alia, the initiatives of the Bill & Melinda Gates Foundation, the GAVI Alliance, WHO, and public-private and product development partnerships. Vaccine safety issues heighten the scope of what is needed for a vaccine to be publicly acceptable. Because vaccines are largely given to healthy individuals to protect against a future threat of disease, safety is paramount, a concern that substantively affects an already complicated and costly research and development process. Achievement of an acceptable balance of benefit and risk is an enormous challenge; no vaccine can be exempt from all risk of adverse events. Furthermore, when safety issues are raised, gathering the appropriate data can take years and, during that time, anxieties cannot be disquieted. Nonetheless, the evidence unequivocally supports that immunisation is an absolutely fundamental component of global efforts aimed at efficient and cost-effective improvement of public health.

However, the difficulties in establishment of robust and sustainable policies and financing of global immunisation programmes cannot be underestimated; these issues are reviewed in the fourth paper in this Series.[5] As we look to the next decade and beyond, the global landscape of vaccinology is undergoing substantial changes. A third of the world's population lack the basics of daily living and, by the middle of this century, the world population will exceed 9 billion.[6] The world is more closely networked than ever before and the burgeoning amount of air travel means that the spread of any pathogen across the globe can occur within hours.

The spread of information—and misinformation—has also changed through the internet and blogging. Advocates of immunisation should continue to interact broadly with society, but this engagement should be keenly appreciative of the contemporary and changing media environment. A high priority is placed on freedom of speech, irrespective of the accuracy of its content. Misinformation about immunisation, whether intentional or not, needs to be countered urgently to help recipients of vaccines seek reliable facts and trust health professionals. Although the benefits of vaccines are unequivocal and based on rigorous scientific evidence, how should advocates of immunisation respond to people who are sceptical or even aggressively opposed to immunisation? Antipathy, distrust, fear, and even outright rejection of scientific evidence are unwelcome to its proponents, but should not come as a surprise. Lessons from other contemporary challenges, such as those posed by climate change or genetically modified organisms, could help with building public trust in immunisation. In informing the public, advocates need to achieve a balance between the benefits of immunisation and acknowledgment of possible adverse outcomes.

Although evidence should inform public discussion and policy development, perception is to a great extent in the hands of consumers and the media. Championing the benefits of scientific evidence to a world made up of individuals of differing age, sex, religious affiliation, culture, education, socioeconomic status, and aspirations is a tall order. Nonetheless, professional education is paramount as advocates of immunisation strive to distinguish scientific evidence from misinformation and strengthen public confidence in vaccines, which is an aim of this Series. Important initiatives have already been taken—for example, the US Institute of Medicine has addressed key issues of the measles, mumps, and rubella (MMR) vaccine and autism, thiomersal and neurological developmental disorders, multiple immunisations, hepatitis B and neurological disorders, and anthrax safety, and has set up a national vaccine safety board.[7]

But the provision of clear, concise, and authoritative information is not enough. Horizons should be broadened with an eclectic range of expertise: for example, anthropologists can help to improve understanding of the cultural basis of behavioural responses, including religious extremism; validated questionnaires developed by social scientists can be used to probe issues of risk perception that are not tractable through quantitative approaches; and evolutionary biologists can explain the theories underpinning altruism and cooperation, which are major issues affecting herd immunity. In the next decade, information for the public needs to be systematic, through knowledge of our strengths and weaknesses, comprehensive, through inclusion of all scientific expertise, and credible, through understanding of how to generate trust and communicate effectively with policy makers and the public.

In the first paper of this Series, we discuss the challenges posed by antigenic variation of bacteria, viruses, and parasites, and the reciprocal challenge of

eliciting protective immune responses in genetically diverse individuals and differing geographical environments.

Pathogen diversity

The diversity of pathogens, whether based on genotype or phenotype, is astonishing and poses enormous challenges with respect to treatment and prevention of microbial diseases. Although the practice of variolation to prevent smallpox dates back many centuries, vaccines effectively came of age in the late 19th and early 20th centuries, in the golden era of bacteriology. The germ theory—the idea that particular species of microbes caused specific diseases—was axiomatic to the successful development of the earliest vaccines, and paved the way for use of whole organisms (eg, for pertussis and tuberculosis) or microbial toxins (eg, tetanus and diphtheria toxins) to induce protective immunity. For many decades, microbial diversity did not cause vaccine failure. Early vaccines stood the test of time because protective immunity was directed to invariant antigens. With the discovery and characterisation of viruses, such as influenza and poliovirus, the need to consider antigenic variation became clear. In the early 1950s, Sabin and colleagues[8] showed that immunisation with each of three distinct variants of poliovirus was needed to induce comprehensive protection. The antigenic shift and drift of influenza A viruses provided another example of the need to base effective vaccine strategies on a detailed knowledge of antigenic variation, specifically the neuraminidase and haemagglutinin antigens. Research on parasites, such as those causing malaria, trypanosomiasis, and leishmaniasis, also revealed extensive antigenic diversity.[1] At the time of writing, no vaccine has been licensed to prevent any human parasitic disease, despite the devastating morbidity and mortality wrought by these diseases.

For most of the diseases that can be prevented by existing vaccines, the target antigens are constant and do not vary over time or place, as exemplified by strain-specific vaccines against MMR, yellow fever, tetanus, diphtheria, and *Haemophilus influenzae* type b. Vaccines against poliovirus (live or killed) are only slightly more complicated than are strain-specific vaccines because three variants need to be included, but these multivalent formulations have remained highly effective worldwide, and efforts towards global elimination of poliomyelitis are ongoing. Occasional outbreaks of poliomyelitis have been caused by recombination between pathogenic vaccine-derived polioviruses and enteroviruses, which is an interesting model of viral evolution and emergence.[9] By contrast, vaccination against influenza A is complicated by antigenic variation in the target vaccine antigens.[10] Hence regular changes in the formulation of the vaccine are needed, but, at any one timepoint, few viral variants are in global circulation so a viable strategy is feasible. The major problem, as recently shown by the influenza A H1N1 pandemic, is that existing technology to make the vaccine is not fast enough to keep pace with the rapid spread of a pandemic strain.[3]

For many important pathogens, vaccine development needs to overcome the problem that many of the relevant candidate vaccine antigens are present in only a proportion of disease-causing strains of the species or, because of allelic variation, the chosen antigens induce protective immune responses that are not cross-protective against all strains. Therefore, vaccine development in the next decade and beyond needs to be based on a detailed understanding of the origins, maintenance, and dynamics of pathogen diversity and the relevant evolutionary and population biology underpinning this microbial variation (panel 1, panel 2, figure 1).

Panel 1: Evolution of pathogen diversity

Life forms date back at least 3·5 billion years. Microbial species, including those for which new or improved vaccines are urgently needed, evolve continuously: "....nothing in biology makes sense except in the light of evolution".[11] Today's microbes, including pathogens, evolved from ancestral forms that over vast periods of time were subject to sequential losses and gains of DNA through mutation and genetic exchange. All microbes, including pathogens, have been selected on the basis of their biological fitness, a composite property indicative of the replication and survival of a microbe, captured in the term basic reproductive rate (R_0). In any population of microbes, R_0 shows the number of surviving progeny produced, on average, by each individual microbe. To persist, R_0 of a microbial population must exceed one and the extent to which it does so is a quantitative measure of fitness. Importantly, many of the products of genes for adaptation are surface-expressed or secreted molecules that are vaccine candidates. The surface location or release of such molecules contribute to microbial fitness within the host, but microbes are also subject to selective pressures exerted by the host innate and adaptive immune mechanisms. Thus, host immune selection provides a major evolutionary drive for diversification of surface-located pathogen molecules. Unsurprisingly, the capacity of microbial surface structures to vary is subject to selection. The different strains that make up the population of a particular pathogenic species differ in genotype (gene content and organisation) and these variations have phenotypic consequences, including the antigenic variation that is such a challenge for vaccine development. Two major factors determine variation in microbial populations—mutation and genetic exchange (panel 2, figure 1).

Glycoconjugate vaccines

The different levels of vaccine complexity needed with respect to antigenic variation, and the implications of such complexity for vaccines, is exemplified by glycoconjugate vaccines, each of which is made from

Panel 2: Generation of diversity in asexual microbial populations by mutation and genetic exchange

Figure 1 shows how diversity evolves in asexual microbial populations (which contrasts with sexual reproduction of many parasites, yeast, and hosts, including man). Over time, many phenotypic variants arise, only one of which is depicted (variant A'), through accumulation of mutations in the ancestral organism (variant A). Most of the progeny of the ancestral organism will not be variants and genetic divergence of the population occurs slowly. The resulting population of variants is clonal, meaning that the diversity can be traced to a common ancestor. But many microbial populations are non-clonal, meaning that variations occur through lateral genetic transfer. Any life form can provide genetic novelty through lateral genetic transfer (variant B), although the most frequent source is within-species transfer (variant C). For example, lateral genetic transfer is needed for acquisition of novel surface antigens such as the shifts in haemagglutins or neuraminidases in influenza, and for switching of capsular antigens in the bacterium *Streptococcus pneumoniae* or in the variant adhesins (*var* genes) of the malarial parasite *Plasmodium falciparum*. Lateral genetic transfer is fundamental to understanding the diversity of microbial populations and, importantly, is a mechanism that greatly accelerates the spread of genetic diversity within populations of pathogens.

The amount of diversity is determined by two factors, the age of the species and interstrain genetic transfer. First, the more recent that speciation has occurred, the less time available for the species to accumulate genetic variation through mutations. Second, interstrain genetic transfer (recombination) profoundly affects the amount and rapidity of genetic divergence between strains. Recombination not only accelerates genetic divergence, since classical mutations introduce variation quite slowly, but it also impedes prediction of genetic associations. Loss or gain of DNA (or RNA) complicates the relatedness of progeny to their ancestors in a clonal population, resulting in a non-clonal population. This disruption of clonal population structure through genetic transfer leads to discordant associations of antigens, complicates predictions of antigen coverage for a multivalent vaccine, and requires detailed analysis of individual strains. To index the diversity in the strains in a population of pathogens, methods need to be able to distinguish variations between strains and establish the relatedness of one strain of a species to another. To this end, nucleic acid sequencing has been pivotal and can be used to characterise very large numbers of strains of any pathogenic species. The compilation of sequence data from many isolates provides a powerful profile of the evolved and evolving diversity of the natural population, and the implications of this diversity for potential vaccine antigens. For diseases in which future vaccines will need to cope with substantial antigenic variation, researchers need to rethink strategies for antigen discovery and development, and the associated regulatory framework and epidemiological surveillance.

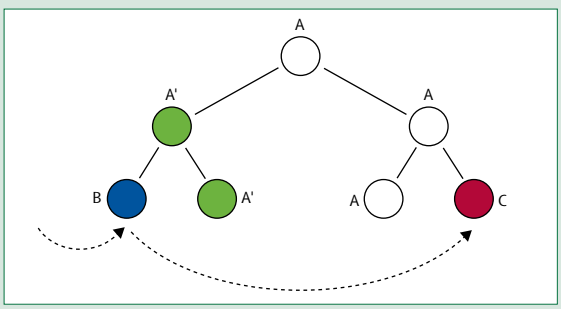

Figure 1: **Generation of diversity in microbial populations**
This figure shows the processes outlined in panel 2. An ancestral organism A (white) mutates and results in a phenotypic variant A' (green). The solid lines represent many generations. The interrupted lines represent lateral genetic transfer from any life form for variant B (blue) and within-species genetic transfer for variant C (red) of DNA (or RNA in the case of some viruses).

different but stable capsular polysaccharides. In the case of *H influenzae* type b, only strains expressing serotype b capsule, the target antigen for protective immunity, show associations with systemic disease that are of major public health importance.[12,13] Thus, glycoconjugate vaccines against *H influenzae* type b are fairly uncomplicated; the type b capsular antigen is stable over time and in different countries. A legitimate concern is that genetic exchange between different strains of the species might result in capsule switching, but, in the two decades since introduction of these glycoconjugate vaccines, there has been no indication that capsule switching is a substantial threat.[14]

By contrast, concerns are justified with respect to glycoconjugate vaccines against *Neisseria meningitidis*, which became available in 2009.[15] At least six of the 14 different *N meningitidis* capsular antigens cause potentially fatal diseases, and the epidemiology of infection (carriage and disease) is subject to variations over time and geography.[15] For example, in Africa, capsular serogroup A and, to a lesser extent, serogroup C were the most important causes of epidemics and outbreaks of invasive meningococcal disease until the 1980s.[16] However, subsequently, strains expressing W and X capsular polysaccharides[16,17] have become important causes of mortality and morbidity. Furthermore, prevention of diseases caused by capsular serogroup B strains—the major causes of invasive meningococcal disease in Europe, the Americas, and Australasia—is problematic because glycoconjugate vaccines against serogroup B, which are similar to those now licensed for other serogroups (A, C, W, and Y), are limited by poor immunogenicity and safety concerns.[18] These considerations have resulted in research to develop a vaccine that is not based on targeting the serogroup B capsular polysaccharide.[19]

Prevention of *Streptococcus pneumoniae* infections is arguably the most complex future challenge to development of glycoconjugate vaccines because serious disease is associated with strains making any one of many antigenically different capsular polysaccharides. Thus, the inclusion of many different antigens (up to 13 capsular polysaccharides, each conjugated to a carrier protein) is needed to achieve broad coverage. The major variable for glycoconjugate vaccines against *S pneumoniae* is the changing prevalence of serotypes by geographical location.[20] Thus, the challenge for vaccine developers is to consider how many antigens (different capsular polysaccharides) should be included, and how these formulations can be modified to cope with geographical variations. Another important issue, well documented for *S pneumoniae* but also applicable to other glycoconjugate vaccines, is that immunisation induces herd immunity by reducing human carriage and spread,[21] but only to strains expressing capsules included in the vaccine.[22] Thus, vaccine selection pressure can result in altered carriage (serotype replacement) in which disease results from pathogenic serotypes that are not included in the vaccine.[22,23] This important factor merits close scrutiny through appropriate epidemiological monitoring, and has stimulated research to develop pneumococcal vaccines with formulations including one or more antigens to provide universal coverage.[24]

Antigenic variation of HIV-1 and *Plasmodium falciparum*

A dominant future challenge is to develop vaccines against major pathogens, such as HIV and *P falciparum*, which have substantial variability of target antigens compounded by unpredictable behaviour over time and geographical location.[25] The number and frequency distribution of antigenic variants should be considered in the initial choice of vaccine antigens, requiring a detailed knowledge of the population structure and molecular epidemiology of the pathogen. The evolutionary factors shaping population structure include the accumulation of mutations and the patterns of interstrain genetic exchange (panel 2), and the effect of natural selection. Furthermore, because of the importance of herd immunity and strain replacement, disease carriage and incidence should be known, and the relevant strains should be characterised by use of robust systems for vaccine typing.

Pandemic HIV-1 represents one of the greatest challenges in vaccine development because it has high antigenic variation and the epidemiology of strains changes over time and location.[26] The biggest obstacle to development of an effective HIV-1 vaccine is the failure to identify one or more viral antigens (immunogen) that stimulate broadly cross-reactive, protective antibodies.[27,28] In natural infection, many different human antibodies are produced to the two major glycoproteins exposed on the viral surface (gp120 and gp41), but very few antibodies are able to neutralise the virus effectively and identification of these antibodies and their cognate viral structures has proved difficult.[29] However, structural biology could pave the way towards rational vaccine design.[30,31] Wu and colleagues[31] screened individuals infected with HIV-1 for high potency neutralising antibodies, and then solved the crystal structure of the viral target glycoprotein (gp120 bound by these antibodies), which is a trimeric spike in its native state. These studies, reviewed by Walker and colleagues,[30] have negated a major concern, namely that achievement of adequate potency of protective immunity would inevitably be traded off against breadth of strain coverage.

The surface proteins of *P falciparum* also have extensive genetic diversity.[32] *P falciparum* causes the form of malaria that is associated with appalling mortality and morbidity, especially in Africa.[33] During its life cycle, the parasite expresses different antigens specific to each of its several stages. Furthermore, the longstanding co-evolutionary history with its human host has resulted in immune selective pressure manifested in extensive polymorphisms of its surface antigens.[32] Both mutation and genetic exchange (the parasite reproduces sexually) contribute to generation of the dynamic diversity that makes *P falciparum* a moving target. The problem is that vaccines directed against a subset of surface antigens, an exception could be the circumsporozoite antigen, might provide only a time-limited solution as novel variants rise in prevalence because of vaccine selection pressure. Consequently, vaccine development and the associated clinical trials have to take into account the distribution and dynamics of antigenic variations in endemic populations.[34] In the design of clinical trials of candidate vaccines, variant-specific efficacy needs to be a key endpoint and, therefore, molecular epidemiological studies should be done before development and testing of vaccines. Similar principles of study design for complex vaccines will apply to other pathogens, including viruses such as dengue virus, hepatitis C virus, and HIV, and the multivalent formulations envisioned for prevention of bacterial diseases such as *Staphylococcus aureus*, *Escherichia coli*, and *N meningitidis* serogroup B (panel 3[19,35]).

Human diversity: induction of potent antibody responses to weak immunogenic determinants

Vaccines that are effective after induction of only modest antibody responses have all been developed. To target diseases that have so far escaped vaccine prevention, future vaccines need to elicit appropriate effector and memory responses in diverse populations with maximum safety.

The quest for maximum vaccine safety is leading development away from whole-cell inactivated or live attenuated vaccines and towards subunit or non-replicating recombinant vaccines. These purified vaccines, which are essentially deprived of endogenous danger signals, are intrinsically less immunogenic than are

Panel 3: Implications of antigenic variation in assessment of vaccine effectiveness

Dengue

Dengue flavivirus is a mosquito-borne pathogen with four serotypes. The virus is reported in tropical and subtropical regions with an estimated 50–100 million infections per year and the number is increasing.[36] Sequence variation (30–35%) of the virus is such that vaccination against the variant antigen of one serotype does not provide protection from infection with the other serotypes. Many candidates for dengue vaccines are under development and some have already been investigated in human beings (NCT00875524), but the vaccines might need to elicit neutralising antibodies to each of the serotypes. Furthermore, the antibodies stimulated by the vaccine are likely to be neutralising (protective) against homologous serotypes, but not against heterologous serotypes. Indeed, the partial cross-reactivity induced by the vaccine might actually increase infection to heterologous strains through opsonisation that increases viral uptake, intracellular replication, and disease severity.[37,38] Vaccine development against dengue virus shows how antigenic variation complicates vaccine formulation and poses potential issues with vaccine safety.

Neisseria meningitidis

The poor immunogenicity and safety issues associated with capsular polysaccharide-based glycoconjugate vaccines against *N meningitidis* capsular serogroup B (Men B) disease (meningitis and septicaemia) has resulted in research to develop vaccines based on membrane proteins of this bacterium.[19] For example, one candidate formulation[35] consists of three antigens that are targets for bactericidal (protective) antibodies, which for simplicity are designated antigens A, B, and C. Antigen A shows allelic variation such that antibodies are protective against only a proportion of strains, antigen B is present in few strains, and antigen C is present in all strains but the amount expressed varies and, in some cases, is no longer quantitatively sufficient to sustain antibody-mediated protection.

In view of the rarity of Men B disease (<1 to ≤25 per 100 000 population),[16] a validated surrogate of protection, provided by the bactericidal assay, is needed to estimate efficacy in clinical trials. Clinical trials to test the vaccine and predict efficacy depend on identification of the proportion of individuals who have serum bactericidal activity to one or more of the three antigens after immunisation,[39] assuming that all individuals had no bactericidal antibodies and were therefore susceptible before immunisation. A detailed knowledge of the prevalence of Men B strains is also needed with respect to the three target antigens, which requires a typing scheme to assign any individual Men B strain to one of seven possible vaccine types (VTs): VT-1 (A, B, C); VT-2 (A, C); VT-3 (B, C); VT-4 (A, B); VT-5 (A); VT-6 (B); or VT-7 (C).

A major unknown is whether bactericidal activity to each of the antigens is sufficient to protect against disease. Bactericidal assays are done with strains that are grown in vitro. The antigens that are targets for protective immune responses are subject to changes in expression, for example through phase variation or post-translational modification, and the amount of each target antigen that is expressed in vitro might not correlate with that occurring in the host during infection. Careful consideration should be given to the choice of strains used in immune assays of host responses to estimate efficacy in clinical trials.[39] Another major unknown is the contribution of herd immunity to protection. Trials to assess the effect of a vaccine on carriage and transmission of disease before implementation can be difficult because of the large sample sizes needed. In such cases, with careful prospective planning, efficacy studies of direct (individual) and indirect (herd immunity) protection by the vaccine can be obtained after implementation by comparison of disease rates in individuals who are and are not immunised by use of case control or screening.[40,41] Because the natural population of meningococci evolves quite rapidly, detailed prospective studies of carriage and disease strains should be done to assess the adequacy of coverage and the need for changes in vaccine formulation.

naturally adjuvanted whole-cell or live vaccines.[42] However, many diseases need higher titres of neutralising antibodies to be induced than might be achieved with subunit vaccines, even in schedules with several doses.[43] Thus, specific immunisation strategies need to be developed to increase antibody responses to vaccines through improvement of B-cell targeting and activation (panel 4, figure 2). A role for novel adjuvants is best shown by the major effect of adjuvants on primary responses to influenza A H5N1.[44] Such adjuvants also address, at least in part, the issue of antigenic diversity by eliciting broader responses capable of cross-strain neutralisation.[45] As a rule, the breadth and neutralising potency increases with the antigen-specific antibody affinity.[46] However, polyreactive antibodies might engage in heteroligation, which implies that they could have an unsuspected role in viral neutralisation.[47]

Most vaccines have been developed for intramuscular or subcutaneous administration, but injection safety remains an issue worldwide and delivery without needles would improve the safety and logistics of immunisation.[48] Alternative routes of immunisation would also be immunologically relevant because pathogens naturally invade their hosts and disseminate through mucosal or skin surfaces. However, elicitation of protective immunity on mucosal surfaces has proven tricky: potent inflammation-inducing adjuvants are generally needed to overcome mucosal barriers while avoiding potentially harmful excess inflammatory reactions.[49,50] However, basic immunological knowledge is providing new insights into how the regulation of tissue-specific lymphocyte trafficking and differentiation could be used to induce protection directly at the mucosal surface.[51] The skin is an attractive route for

vaccine administration, being densely populated by antigen presenting cells capable of efficiently migrating towards the draining lymph nodes.[52] The intradermal route could be revived by the development of easy-to-use delivery devices.[53] An interesting societal issue will be whether the induction of superficial skin or soft-tissue inflammatory reactions, effects obvious to immunised individuals, might limit vaccine acceptance.

Even the most potent vectors or adjuvants given by the best possible route will not transform weakly immunogenic polysaccharides or proteins into potent vaccine antigens. Thus, the antigen itself might have to be modified. The success of this approach was shown by glycoconjugate vaccines, which elicit B-cell responses of increased potency by provision of immunogenic epitopes to CD4 T cells.[42] An important future goal is to combine high-resolution structural analysis and immunobiological assays to identify the essential antigenic determinants of protection, and thus advance vaccinology from empiricism to the rational design of immunogens.[54]

Instruction of antigen presenting cells towards appropriate T-cell responses

Increasingly, novel immunological assays are directed towards the characterisation and identification of the functional (protective) roles of CD4 and CD8 T cells. Elicitation of appropriate T-cell responses has become a key milestone for novel vaccines. A complex combination of appropriate activation and regulatory signals properly spaced in time and location[55] are needed to direct T-cell differentiation along specific effector pathways and towards memory cells (panel 4, figure 2). These signals can be modulated by specific adjuvants and vectors, which might also affect the fine specificity and clonotypic diversity of antigen-specific CD4 T-cell responses[56] and thus modulate the induction of cytotoxic or regulatory CD8 T cells. Thus, most novel subunit vaccines will include immunomodulators to preferentially induce CD4 T-cell differentiation along specific pathways, whereas novel vectors should become available to elicit potent CD8 T-cell responses (panel 4, figure 2).

The level of complexity of T-cell responses implies many challenges, including how to select the vaccine candidates most likely to survive the stringent selection process leading from preclinical trials to clinical trials, licensing, and implementation. Indeed, although the limitations of most animal models are well established, human trials cannot realistically be done for all potential vaccine candidates. Although improved cellular immunological techniques could possibly improve the selection process, they will not circumvent the major limiting factor that blood samples are accessible but not representative of the processes in tissues, nodes, or bone marrow compartments.

Lifelong vaccine-induced protection without repeat boosting

Prophylactic vaccines can only contribute to individual and public health if they induce sustained protective responses. Ideally, vaccine responses should be elicited by a single immunisation and last a lifetime. This objective can indeed be achieved, as shown by smallpox vaccines.[57] However, a lifelong persistence of antibody responses is the exception rather than the rule: in the absence of antigen exposure, vaccine-induced antibodies progressively decline to eventually reach undetectable concentrations.[42] Research has not yet identified precisely why certain antibodies persist for several decades whereas others wane after a few years.

However, evidence now suggests that the type and duration of immune memory might be largely determined by the magnitude and complexity of the innate immune signals provided at induction, opening new perspectives.[58] For example, triggering of both toll-like receptors 4 and 7 induces early programming towards B-cell memory, in both mice and macaques.[59] We now understand that the reactivation of resting memory B cells into immunoglobulin-secreting plasma cells requires both antigen exposure and time. Thus, protection against diseases with a rapid pace of pathogenesis or absence of pathogenic invasion beyond mucosal surfaces requires long-term maintenance of needed of serum antibodies.[60] A new challenge is to identify determinants of the induction, size, and persistence of sufficient pools of antibody-secreting plasma cells, memory B cells, or T cells (panel 4, figure 2), and to define the extent to which these determinants could be modulated by immunisation strategies.

Herd immunity is another important mechanism that might contribute to the maintenance of vaccine-induced protection despite primary or secondary vaccine failures. The success of this approach was shown by the introduction of glycoconjugate vaccines into carrier age-groups (infants, young children, or adolescents).[61,62] It also applies to sexually transmitted diseases such as hepatitis B virus[63] or human papillomavirus infections. According to mathematical modelling and a few studies,[64,65] the best societal use of influenza vaccines could be to target pre-school or school children as the main transmitters, in addition to or instead of elderly people or other high-risk groups in whom vaccine efficacy is often poor. Shifting of vaccine targets from the high-risk groups to the high-transmitter groups, or even vaccination of target groups with little direct benefit, would represent a substantial societal challenge in view of the tension between individual rights and public health.[66]

Limitations of young or advanced age and chronic disease

A major scientific and societal challenge is to develop effective vaccines for individuals in whom the functions

Panel 4: **Immunological challenges for new vaccines**

At the site of injection

To initiate a successful immune response, vaccines need to include sufficient danger recognition patterns to activate local cells that participate in innate responses, such as stromal cells, tissue-resident monocytes, muscle cells, or mucosal cells, to produce chemokines and inflammatory signals (figure 2, label 1). These early signals trigger circulating monocytes, leucocytes, or dendritic cells (label 2) to exit from blood vessels, migrate to the injection site, and provide further inflammatory signals. The combined direct and indirect activation of locally resident or attracted APCs (label 3) should elicit increased uptake of antigen or adjuvant molecules, antigen processing and display by surface MHC molecules (T-cell activation signal 1), expression of activation markers (signal 2), and cytokine production (signal 3). This activation is needed for antigen-decorated, adjuvant-activated APCs to migrate towards the lymph nodes draining the site of injection (label 4). The main immunological challenge for novel vaccines is thus to trigger sufficient local activation signals to elicit the best possible vaccine responses, while avoiding both excess inflammatory reactions and the non-specific activation of bystander immune cells.

In the draining lymph nodes

Soluble antigen or adjuvant molecules reach the capsular sinus of the draining lymph nodes within minutes (free-fluid diffusion), followed a few hours later by locally activated antigen-bearing APCs (label 4). For potent, sustained vaccine responses, both T and B cells need to be induced. Antigen-expressing, activated APCs migrate into the T-cell area (label 5). APCs need to display antigenic peptides on MHC class II molecules to induce the differentiation of antigen-specific CD4 T cells into Th1, Th2, or Th17 effector cells, Tfh cells, or Treg cells, whereas APCs with antigens displayed on MHC class I lead to optimum activation of CD8 T cells (label 6). A sufficient pool of Tcm cells, which constitute a reservoir of antigen-primed memory cells in the skin and nodes, and of ready-to-function Tem cells in peripheral tissues is needed to induce sustained vaccine responses (label 7). Activation of distinct pathways is needed for optimum induction of antibody-producing cells. Vaccine antigens reach the B-cell follicles (label 8) by free-fluid diffusion or channelling by subcapsular sinus macrophages. B cells binding to the antigen surface (signal 1) and sufficient coactivation signals from activated APCs and CD4 helper cells are needed to activate antigen-specific B cells to migrate towards B-cell follicles and induce the germinal center reaction. Through a selection process of proliferation, hypermutation, differentiation, and affinity maturation, which is affected by the nature and intensity of B-cell activation, B cells differentiate into antibody-secreting plasma cells or memory B cells (label 9). Large pools of long-lived antibody-secreting plasma cells surviving in specific bone marrow niches, and a sufficient reservoir of antigen-specific memory B cells ready to differentiate into antibody-producing cells within a few days, are needed to generate sustained vaccine responses.

APC=antigen presenting cell. Th=T helper cell. Tfh=follicular T cell. Treg=regulatory T cell. Tcm=central memory T cell. Tem=effector memory T cell.

of the immune system are immature (infants), affected by chronic disorders (diabetes, cancer, or chronic disease of any organ), or declining because of ageing. Effective vaccines in early life need to overcome both immune immaturity, which limits antibody responses and preferentially polarises T cells away from inflammatory responses, and the inhibitory effects of maternal antibodies.[43,67] Furthermore, vaccines should not trigger excess reactogenicity, a challenging issue in early life.[68] The likelihood that high titres of functional antibodies can be elicited within weeks after birth is a remote objective.[43] The best approach is thus to promote early life protection through a combination of maternal immunisation, neonatal immunisation, and development of safe adjuvanted infant vaccines, which is a challenging strategy in view of the risk-adverse context of pregnancy and early life.

Another challenge is to develop vaccines capable of improving vaccine-induced protection in immunocompromised patients, a growing population because of the increased use of immunosuppressive treatments and the spread of HIV infection. Remarkably little is known about how specific anti-inflammatory and immunomodulatory treatments affect immune responses—for example, the inhibitory effect of prophylactic paracetamol on infant vaccine responses came as a surprise.[69] These effects limit the rational design of the best possible immunisation approaches for immunocompromised patients and raise several questions. Could adjuvanted vaccines including more potent immunomodulators prove more effective in certain immunocompromised patients? Could such vaccines prove safe in immunocompromised patients but be too reactogenic in healthy individuals? How could such vaccines be developed in today's stringent regulatory environment without the financial incentive of a large market size?

The elderly population is rapidly growing and needs progress in vaccinology. The estimated benefits of pneumococcal or influenza immunisation in elderly people have been largely overestimated.[70–73] Several mechanisms combine to result in age-associated immune frailty:[43,74] impaired responses to toll-like receptor-mediated signalling;[75] and progressive waning of cell-mediated immunity because of reduced thymic output and progressive expansion of dysfunctional terminally differentiated T cells driven by chronic viral infection.[76] Potent adjuvants could potentially improve immunogenicity through increasing responses to toll-like-receptor-mediated signalling. Virosomes, MF59, AS03, and other adjuvants indeed improve immunogenicity to influenza vaccination in elderly people, but do not restore immunogenicity to that of younger adults, suggesting the existence of other crucial factors.[77] Whether vaccine prevention can be improved by novel vaccines or would need strategies to slow the immune senescence process is a challenging issue.

Immunological safety of vaccines

The potent adjuvants that vaccinologists strive to develop and clinicians desire to have will not be used unless they prove safe.[2] From an immunological perspective, some key features of adjuvant safety are beginning to unravel. At the site of injection, inflammatory reactions are indicative of the onset of innate immunity, as shown by the number and type of recruited cells, the activation of these cells, and the associated cytokine release (panel 4, figure 2).[78] Consequently, adjuvants eliciting less intense reactions across a long period might show a better reactogenicity profile than do those with a hit-and-run

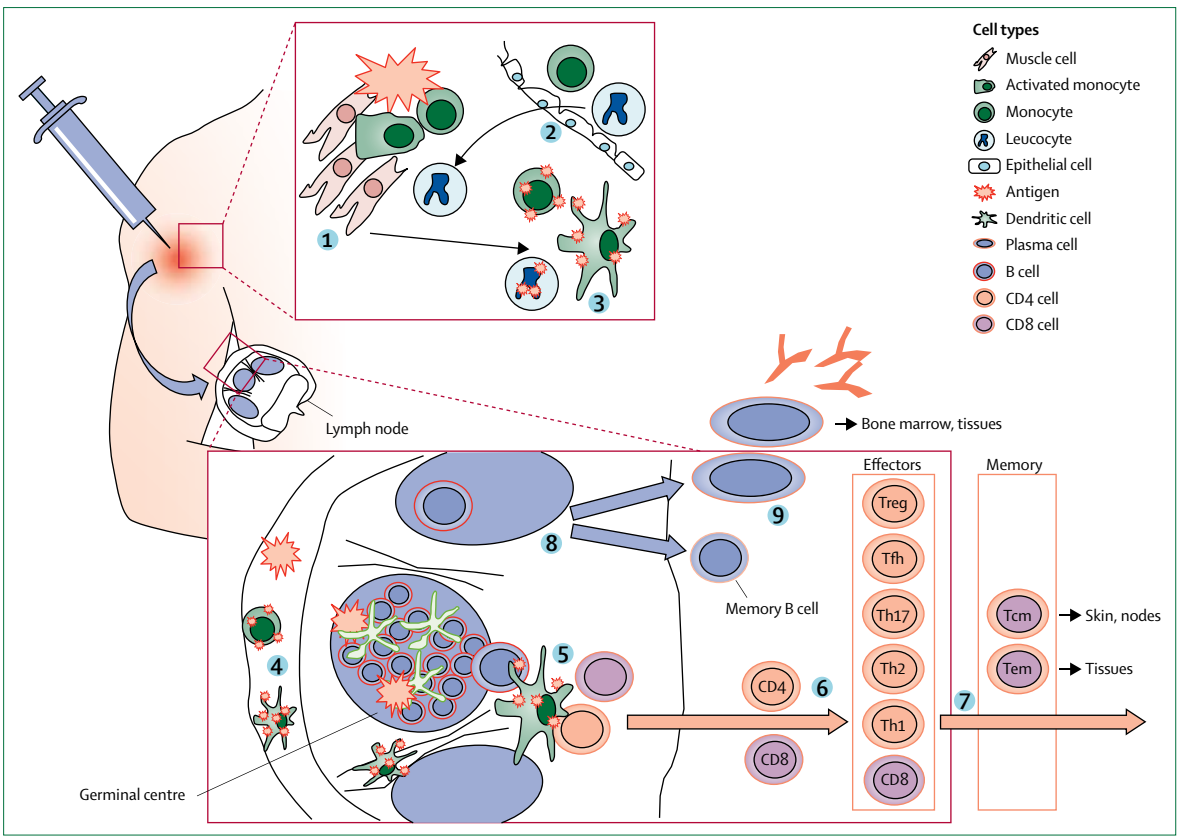

Figure 2: **Immunological challenges for new vaccines**
This figure shows the processes outlined in panel 4. Treg=regulatory T cell. Tfh=follicular T cell. Th=T helper cell. Tcm=central memory T cell. Tem=effector memory T cell.

profile (ie, eliciting a highly intense reaction in a short period). An unmet challenge will be to learn how to translate preclinical observations about the type and magnitude of innate responses to the expected reactogenicity pattern in individuals differing in their antigen experience, health problems, and genetic background. In the draining lymph nodes, bystander activation of potentially autoreactive B or T cells should be avoided because of possible autoimmune manifestations.[79] This aim is likely to be best achieved with formulations deprived of polyclonal activation capacities, and by restriction of antigen presenting cell activation to the monocyte-derived dendritic cells generated at the site of injection rather than those residing in the lymph nodes. Avoidance of the systemic dissemination of immunomodulatory signals also seems crucial. Novel imaging techniques that allow in-vivo assessment of the fate of vaccine components should prove useful to characterise and select formulations with the most promising immunological safety patterns.

From mass immunisation to personalised responses: environmental and genetic factors

The one-size-fits-all approach is not sustainable in vaccine prevention of diseases. In the past three decades, vaccines have been shown to elicit variable responses in distinct geographical environments. For example, the same conjugate vaccine against *H influenzae* type b (PRP-D) proved effective in Finland but not in Alaska, and Chilean infants raised three-times higher antibody responses to immunisation than did Belgian children.[80] Subsequently, rotavirus vaccines that were proven effective in Europe, Latin America, and the USA were much less immunogenic in low-income countries.[81] Disentangling the relative contribution of varying epidemiology patterns, environmental factors, and host genetic factors contributing to the success of a vaccine, or to adverse vaccine outcomes, is a major challenge.

The potency of the immune system resides in its highly polymorphic nature, enabling sufficient immunological diversity to overcome many diverse pathogens. The severe or fatal outcomes of infection in otherwise healthy immunocompetent hosts result from genetic predispositions mediated by mutations in specific immune genes.[82] This genetic basis implies that researchers could predict the infections that individuals are genetically destined to be at risk from, or at least those infections that are severe in rare cases, and thus only these individuals would be selectively protected. For example, identification of the small proportion of

individuals who fail to rapidly clear viruses such as hepatitis B virus or human papillomavirus—and are thus at high risk of chronic infection or cancer[83]—would allow immunisation strategies to focus on high-risk individuals. In theory, genetic screening for the likelihood of severe complications from most or all vaccine-preventable pathogens could thus generate personalised recommendations for immunisation.

The diversity of the immune system similarly affects vaccine responses. Millions of single nucleotide polymorphisms, and even more genetic variants, have been identified. The successful development of pharmacogenomics has prompted probing of how host genetic markers might result in variations of vaccine-induced responses.[84] This research is expected to identify gene polymorphisms that predict the likelihood that a vaccine will be successful or have adverse outcomes of either vaccine failure or adverse events.[84] Epigenetic studies might help to better understand how environmental factors can affect innate and adaptive immune responses. This work is still in its infancy but holds promise, especially when combined with novel system vaccinology approaches.[85,86]

Paradoxically, however, the global successes of mass immunisation strategies contrast with the largely recognised failure of strategies targeting individuals at increased risk of complications, whether from underlying disease or treatment.[87,88] Such a move from community-based towards personalised genetic-driven immunisation strategies would thus raise major new challenges: high-risk individuals who should be immunised against specific pathogens, or should not be immunised because of increased risk of adverse event, would need to be identified; relative risks would need to be communicated to high-risk individuals; personalised recommendations would need to be generated for these high-risk individuals; and immunisation services capable of reaching all high-risk individuals, who would no longer be indirectly protected by herd immunity, would need to be implemented. Furthermore, individuals defined as low risk by genetic analysis might become high risk when they become immunocompromised by disorders or treatments. Replacement of the existing immunisation menu with à la carte vaccinations would probably be extremely costly, and thus would initially be restricted to a few novel expensive vaccines with potentially higher efficacy but also higher risk of adverse events than with existing vaccines. Interestingly, developments in personalised immunisation might be driven by the increasing consumer demand for personalised medical approaches that maximise the likelihood of benefits but mitigate the risks of severe adverse events.

Conclusions

Compared with their human hosts, microbial populations are greater in number, have higher rates of replication, generate more mutations, and have promiscuous mechanisms of genetic exchange. These factors underpin the diversity of microbial genotypes and phenotypes, and are major factors in the adaptive potential that determine their commensal and virulence behaviour. In the past, the major contributions to vaccine research were made by microbiologists who combined detailed knowledge of microbial diseases with no small measure of empiricism to choose components that could induce protective immunity. However, many of the most challenging pathogens are characterised by several mechanisms of antigenic variation, allowing evasion of host immune responses. For these pathogens, host-microbial interactions are highly complex: natural infection often does not confer adequate immunity to protect against future exposure. In the future, immunology will be a cornerstone of our efforts to understand in detail what is needed to formulate and present microbial components so as to engage innate and adaptive host immune responses efficiently and safely. To that end, reductionist approaches, especially those using in-vitro systems, have increased our understanding of the role of dendritic cells in innate immunity, and of T and B cells in adaptive immunity. But reductionist science can fall short of capturing the highly relevant complexity that characterises the combinatorial interplay between host genetic polymorphisms and environmental factors; we are, for example, only just beginning to unravel the crucial dialogue between commensal microbes (host microbiota) and immune responsiveness.[89]

Contributors

ERM and C-AS equally contributed to conception, writing, and revision of the report.

Conflicts of interest

ERM has received honoraria for work as a board member for Novartis and GlycoVaxyn, and as a consultant for Novartis. C-AS's institution has received grants from GlaxoSmithKline, Sanofi Pasteur, Nasvax, and DBV Technologies; and travel and accommodation expenses from GlaxoSmithKline and Sanofi Pasteur. C-AS and C-AS's institution have received royalties for the patent for Viavac; and C-AS has patents, which have not generated royalties, with Sanofi Pasteur and DBV Technologies.

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New Decade of Vaccines 2

Vaccine discovery and translation of new vaccine technology

Rino Rappuoli, Steven Black, Paul Henri Lambert

An unprecedented increase in new vaccine development has occurred over the past three decades. This activity has resulted in vaccines that protect against an increased range of vaccine-preventable diseases, vaccines that reduce the number of required injections, and vaccines with improved safety and purity. New methods of discovery, such as reverse vaccinology, structural biology, and systems biology, promise new vaccines for different diseases and efficient development pathways for these vaccines. We expect development of vaccines not only for infectious diseases in children but also for healthy adults, pregnant women, and elderly people, and for new indications such as autoimmune disease and cancer. We have witnessed a concomitant development of new technology for assessment of vaccine safety to rapidly identify potential safety issues. Success of these new approaches will depend on effective implementation of vaccination programmes, creative thinking on the part of manufacturers and regulators as to how best to ensure that safe and effective vaccines are available in a timely manner, and improvement of public awareness about the benefits and risks of new vaccines in a way that encourages confidence in vaccines.

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

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Introduction

On May 8, 1980, the World Health Assembly certified the world free of naturally occurring smallpox.[1] Since then, an unprecedented rise in new vaccine development has occurred (table 1).[2] This activity has resulted in vaccines that provide an increased range of vaccine-preventable diseases including conjugate vaccines for encapsulated bacteria such as *Haemophilus influenzae* type b, pneumococcus, and meningococcus, new combined vaccines that allow a reduced number of injections, new adjuvants such as MF59 and AS03, highly purified vaccines to replace older vaccines such as acellular pertussis instead of whole-cell pertussis, and technologies that offer the possibility of fast vaccine development. Furthermore, development of new technology for assessment of vaccine safety has occurred concomitantly.

We review examples of new technologies for the development and preclinical and clinical assessment of vaccines. We have selected historical examples, technologies for vaccine development, safety-assessment issues, and methods that are representative of current research and are likely to move vaccinology forward.

Vaccine development

Early vaccines

A common characteristic of new vaccines is their high level of safety compared with many older vaccines that were developed (table 2); these vaccines were often crude preparations that were associated with safety concerns (table 3). The first rabies vaccine developed by Louis Pasteur, in which the virus was grown in rabbit brain tissue, not only induced immunity against the virus, but also autoimmune disease in up to one in 3000 immunised children.[6] Other similar examples include the old smallpox vaccines, which were occasionally associated with disseminated vaccinia, and oral polio vaccines, which have been associated with rare cases of vaccine-associated paralytic polio (1·1 cases per million first doses).[7] In the past, some accidents were a result of suboptimum manufacturing, as was the case in the so-called Cutter incident;[5] inactivated polio vaccine preparations were not fully inactivated and were associated with 56 cases of paralytic poliomyelitis and five deaths. All of these vaccines have either been discontinued, replaced with safer alternatives, or are now produced with improved technology and quality control. These early vaccines were developed through isolation, attenuation, or inactivation of the causative organism, and use of complex and sometimes incompletely characterised products. However, although crude, this approach was effective for eradication of smallpox and virtual elimination of diseases such as diphtheria,

Key messages

- An unprecedented rise in new vaccine development has occurred over the past three decades, with resultant substantial declines in disease burden and mortality.
- Vaccines have typically been developed with empirical approaches, but newer methods of discovery, including reverse vaccinology, structural biology, and systems biology, promise a more efficient developmental pathway.
- Vaccine targets should expand beyond diseases of childhood to include healthy adults, pregnant women, and elderly people, and new indications such as autoimmune disease and cancer.
- Concomitant with the development of new technology for vaccine development, we have also witnessed development of new methodologies for vaccine safety assessment to rapidly identify any possible safety issues. However, these methods have not improved public confidence in vaccines.

	Cell culture	Recombinant DNA, virus-like particles	Conjugation	Combinations	New adjuvants
1980s	Rabies	Hepatitis B	Hib	..	..
1990s	Japanese encephalitis, varicella, hepatitis A, rotavirus	Acellular pertussis Lyme	Men C	DTP-Hib Hib-hepatitis B DTaP-Hib	Influenza
2000s	Live influenza, rotavirus, herpes zoster, H1N1 influenza	HPV	PnC-7 PnC-10 PnC-13 Men ACWY	Hepatitis B and hepatitis A; DTaP-IPV and hepatitis B; Men ACWY; MMRV	HPV H1N1 influenza

Hib=*Haemophilus influenzae* type b. Men C=meningococcus group C conjugate. DTP=diphtheria, tetanus, and pertussis. DTaP=diphtheria, tetanus, and acellular pertussis. HPV=human papillomavirus. PnC=pneumococcal conjugate. Men ACWY=meningococcal conjugate for groups A, C, W-135, and Y. IPV=inactivated polio vaccine. MMRV=measles, mumps, rubella, and varicella combination.

***Table 1*: New and improved technologies and resulting vaccines (from 1980s to 2000s)**

	Description	Advantages	Drawbacks	Examples
Killed microorganisms	The causative agent is inactivated by chemical or physical treatments	Efficacious	Some pathogens are difficult or almost impossible to cultivate in a scalable setting; regulatory authorities require high safety and quality standards for all new vaccine formulations, so obtaining approval might be difficult	Polio vaccine (eg, developed by Jonas Salk); influenza vaccine; rabies vaccine; oral cholera vaccine
Live attenuated microorganism	The causative agent is live, but it has lost the ability to cause the disease	Efficacious; can induce a protective immune response	Some pathogens are difficult or almost impossible to cultivate in a scalable setting; regulatory authorities require high safety and quality standards for all new vaccine formulations, so obtaining approval might be difficult	Polio vaccine (developed by Albert Sabin[3]); intranasal influenza vaccine (cold adapted); MMRV vaccine
Subunit	Vaccines contain purified portions of the causative agents	Toxins are inactivated chemically. If not properly inactivated they can cause disease (eg, several accidents in the 1950s with diphtheria not fully inactivated[4]); such inactivated vaccines cannot provoke the disease; if recombinant forms of the selected components are used, the pathogen need not be cultivated	Identification of the few protective components from the pool of molecules in the pathogen is usually complex and time consuming	Diphtheria, tetanus, and pertussis toxoids; hepatitis B vaccine; acellular pertussis vaccine
Subunit conjugated	A polysaccharide component of the causative agent is chemically linked to a protein carrier	The conjugated polysaccharide, which is poorly immunogenic on its own, becomes immunogenic	Need to grow the pathogen in vitro to obtain the capsular polysaccharide; capsule not always immunogenic; too many capsule types	Hib vaccine; PnC vaccine; Men ACWY vaccine

MMRV=measles, mumps, rubella, and varicella combination. Hib=*Haemophilus influenzae* type b. PnC=pneumococcal conjugate. Men ACWY=meningococcal conjugate for groups A, C, W-135, and Y.

***Table 2*: Different approaches to vaccine design in the pregenomic period through application of Louis Pasteur's principles**

poliomyelitis, and tetanus as public health problems from most of the world. Although we continue to strive to improve existing vaccines, current vaccines are highly effective and safe public health interventions.

Conjugate vaccines

A striking increase in new vaccines and new vaccine technologies began with the development of a hepatitis B vaccine with recombinant DNA technology,[8] the application of glycoconjugation for polysaccharide vaccines, which resulted in the development of the conjugate *H influenzae* type b vaccine in 1987,[9] and application of improved cell-culture technology. Panel 1 shows the progression of vaccine technologies.

Although polysaccharide vaccines had been available for pneumococcus, meningococcus, and *H influenzae* type b before 1987, their immunogenicity was low in young children, and their inability to induce immunological memory resulted in only a short-term protective effect.[10] Soon after the introduction of conjugate *H influenzae* type b vaccines into vaccination programmes, researchers realised that conjugate vaccines not only provided a direct protective effect for vaccinated individuals but they were able to interrupt circulation of the organism through reduction of colonisation, which resulted in herd immunity with protection of non-vaccinated individuals and near elimination of the pathogen in all countries where routine vaccination had been introduced.[11] Similarly, when the same technology was applied to develop a seven-valent conjugate vaccine against pneumococcus, routine vaccination resulted in near elimination of the seven vaccine serotypes in the

population, which not only protected vaccinated children but substantially reduced disease caused by these serotypes in unvaccinated adults.[12] Similar herd effects have been reported for meningococcal C conjugate vaccine.[13] The public health effect of this technology has been enormous, with the potential to prevent almost 1 million deaths a year caused by acute lower-respiratory-tract infection with routine use of the pneumococcal conjugate vaccine alone.[14]

New technology has also resulted in the introduction of purer vaccines with remarkable safety profiles. Acellular pertussis vaccines have substantially less reactogenicity than do the old whole-cell vaccines.[15] The potential to use cell culture to produce influenza vaccines has provided means with which to avoid any risk to people with egg allergy through elimination of risk related to contamination with egg-derived proteins; this technique also offers the potential to produce influenza vaccines quickly in response to a pandemic.[16]

Development of adjuvants

Early on in the development of vaccines, researchers recognised that for some diseases, antigens alone did not provide optimum protection. Live vaccines, such as those used for measles, were developed to mimic natural infection and induce a strong immunological response without the risk of adverse effects associated with killed vaccines or natural infection. Adjuvants were developed for other diseases, which, when given concomitantly with an antigen, induced a stronger immune response. Until recently, the only adjuvant in routine use was alum (aluminum salt), however, for many diseases, this adjuvant was insufficiently active. New adjuvants have now been constructed, each with specific properties designed to induce a stronger and broader immune response to prevent a specific disease (table 4). Importantly, these new adjuvants do not induce clinically significant adverse effects. Large follow-up studies[17] have shown some of the new adjuvants, such as MF59, to be safe. Other adjuvants, such as AS04, have also been shown to be safe in prelicensure studies and large post-licensure studies of this adjuvant are in progress.[18]

Selection of vaccines

In any vaccine, the selection of antigens is a crucial step. In the past, although a rational approach was used, vaccine antigens were identified largely with empirical approaches. However, empirical methods were limited by the fact that some pathogens did not have easily identifiable immunogenic or protective vaccine antigens. Additionally, some identified target antigens seemed to be unsafe or poorly immunogenic, such as the polysaccharide capsule of meningococcus type B.[19] Genomic sequencing of many pathogens has completely changed this situation. Knowledge of the genome of an organism can now be used to develop vaccines, for example by application of reverse vaccinology (the use of genomic information of an organism to identify potential antigenic targets, which cannot be identified with classic techniques).[20] This concept has helped with the identification of new vaccine antigens which offer the potential for protection against some organisms, such as meningococcus type B, for which no vaccine had been previously available. Reverse vaccinology can also be combined with new adjuvants that allow the type of immune response required for protection to be targeted.

Additionally, the application of structural biology to vaccinology—structural vaccinology—could boost the development of vaccines against diseases in which other approaches have not been successful. Structural biological studies allow the atomic resolution of antigen structure, enabling rational design of specific target epitopes for use as vaccine candidates[21]—structural studies have led to improved understanding of the various mechanisms by which different

	Safety issues	Resolutions
Inactivated polio vaccine	During the Cutter incident,[5] 56 cases of paralytic poliomyelitis occurred with five deaths	Improved monitoring and manufacturing process of virus inactivation
Smallpox vaccine	Generalised vaccinia, encephalitis, myocarditis	Non-replicating vaccinia (modified vaccinia Ankara) in development; disease eradication
Oral polio vaccine	Risk of paralytic disease (vaccine-associated paralytic poliomyelitis) in recipients and contacts	Inactivated polio vaccine now used in most developed countries and introduced in developing countries
Whole-cell diphtheria, tetanus, and pertussis vaccine	Occasional febrile seizures and possible encephalitis	Replaced by purified acellular pertussis vaccines in developed countries
High-dose measles vaccine	High all-cause mortality in girls	Low-dose vaccines are used

Table 3: **Progress in development of vaccines with improved safety**

Panel 1: Expansion of vaccine targets and improvement of vaccine safety with new technologies

Empirical approach
Diphtheria, tetanus, pertussis, rabies, influenza, smallpox, poliomyelitis, BCG

Glycoconjugation
Men ACWY, *Streptococcus pneumoniae, Haemophilus influenzae* type b, group A streptococcus, group B streptococcus, *Staphylococcus aureus*

Reverse vaccinology
Meningococcus group B, group A streptococcus, group B streptococcus, *S aureus*, *Escherichia coli*, *Clostridium difficile*

Next generation technologies
Adjuvants, structural vaccinology, viral vectors, DNA vaccines, RNA vaccines

The oldest vaccines were developed empirically. Vaccines were then developed with glycoconjugation. Existing and potential vaccines are developed with reverse vaccinology. Finally, we list some of next generation technologies that we anticipate will provide new vaccines. Men ACWY=meningococcal conjugate for groups A, C, W-135, and Y.

	Company	Immunological characteristics	Usage in vaccines
Alum (aluminum salt)	Several	Depot and proinflammatory effects	Many vaccines (eg, DTaP-hepatitis B)
MF-59 oil-in-water emulsion	Novartis	Local proinflammatory effects, immune-cell activation	Influenza and pandemic influenza
AS03 oil-in-water emulsion	GlaxoSmithKline	Local proinflammatory effects, immune-cell activation	Influenza and pandemic influenza
AS02 oil-in-water emulsion containing MPL and Q-21	GlaxoSmithKline	Induces antibody and cell-mediated-immune response	Malaria vaccine candidate
AS04 (combination of aluminum salts and MPL)	GlaxoSmithKline	Strong antibody and cell-mediated-immune response, toll-like receptor 4 dependent	HPV vaccine
CpG oligonucleotides	Dynvax, Pfizer	Toll-like receptor 9 agonist	Hepatitis B, cancer, malaria
IC 31 (oligonucleotides plus KLKL 5 bacterial peptide)	Intercell	Toll-like receptor 9 agonist	Influenza, tuberculosis
GLA synthetic lipid A	IDRI	Activates toll-like receptor 4 receptors, induces Th1 CD4 helper cells with broad humoral response	Tuberculosis, leishmaniasis, malaria

DTaP=diphtheria, tetanus, and acellular pertusis. HPV=human papillomavirus. Th=T helper.

Table 4: **Examples of vaccine adjuvant systems**

paramyxoviruses use their attachment glycoproteins to hijack specific protein and glycan cell-surface receptors for viral entry.[22] This information could be used to develop new vaccine approaches for measles.

Several virus or virus-like vectors can be used to deliver vaccine antigens,[23] and they offer the prospect of an expanded range of targets for preventive and therapeutic vaccines. This approach has been used to develop some therapeutic cancer vaccines including a fowl-pox-virus vaccine encoding prostate-specific antigen.[24] Several live vectors have been used as vaccine delivery systems, combining a self-adjuvanted product (vector-dependent) with an immunologically targeted presentation of the expressed vaccine antigens.[23]

Although many vaccine antigens are still identified through empirical techniques, use of genomic and structural biological approaches will probably increase. While the ability to identify possible antigens increases the likelihood of developing a successful vaccine, identification of many possible antigens poses a challenge, because new approaches then need to be used to select which of the possible antigens to take forward for vaccine development. For example, the pneumococcal conjugate vaccines currently in empirical use include the major virulence factor, the bacterial capsule, to develop these vaccines.[25] By contrast, bacterial genomics has provided a long list of new antigens. Refinement of this list down to the best candidate antigens depends on skilful application of several methods; to select these antigens high throughput in-vitro and in-vivo assays including expression systems could be used to establish how they might function and in what proportion of clinical strains they might be expressed. Although an antigen does not have to be a virulence factor, focusing on antigens with a crucial function in pathogenesis or bacterial survival might be useful selection criteria. Other important criteria in the context of pneumococcal vaccines might be antigens, such as adhesins, that could provide herd protection through reduction of organism circulation. The selection process is complicated, and development of models that predict protection through systems biology analyses could help with this process. Systems biology is an integrative method combining knowledge of cytokine and immunological-response patterns to identify markers that predict the safety and effectiveness of vaccines. Ideally, such markers would allow early identification of unsafe vaccine candidates and guide selection of the most effective vaccine combinations.[26]

DNA and RNA vaccines

Although DNA vaccines were initially thought to be a promising technology, studies have yielded disappointing results,[27] with the exception of vaccine strategies that use a prime-boost approach—the immune system is primed most often with a vector coding for one antigen and then a second vaccination is delivered to boost the response with a different vector or the antigen itself.[27] Research into this approach for HIV and cancer vaccines continues.[28] By contrast, work with RNA vaccines seems to offer some promise: messenger RNA vaccines have been prepared with tumour antigens that are highly immunogenic, for use in cancer immunotherapy.[29]

Vaccine safety and effectiveness

Background

In view of the high cost of vaccine development and the long time needed to develop and license a new vaccine, a method for identification of the safest and most effective vaccine candidate for early development would be highly useful. Future studies will probably gather more data during the early period (1–5 days) after vaccination, either through translational studies or phase 1 or 2 vaccine trials to identify early predictors of success; in a study of H5N1 influenza, an increase in virus-specific CD4 T cells measured after dose one accurately predicted a rise in neutralising-antibody concentrations after booster immunisation and

antibody concentrations 6 months later.[30] Additionally, assessment with various microarrays of early events after vaccination, including biomarkers of inflammation and indicators of innate-immunity activation, could also predict vaccine response after vaccination.[31]

In addition to the use of new technologies for development of new vaccines, cost-effectiveness and implementation policy should be considered before undertaking development of a new vaccine. In practice, assessment of cost-effectiveness is complicated by a paucity of information about efficacy of the vaccine and other potential factors, such as induction of herd immunity, which can substantially affect these assessments.[32] In view of the high cost of vaccine development, the availability of official guidance from regulatory and advisory bodies about recommendations for use of a potential vaccine would allow more efficient and effective prioritisation of vaccines for development. The next decade promises to be very productive, as new approaches and technologies are applied to the discovery of new vaccines.

Challenges for vaccine safety

With new developments in vaccine technology come new challenges, including an increased focus on the risk of rare adverse events after vaccination. These adverse events have been associated with a decrease in public confidence in vaccines, an increase in regulatory barriers, and a need to assess safety and efficacy at a global level rather than in a few geographical areas. Future challenges will be not only to develop new and improved vaccines, but to ensure that the full public health benefit of these vaccines is realised by translation of new technologies into effective public health interventions. Assessment of a vaccine for a disease with high mortality such as HIV infection would necessarily take into account any possible safety concerns in view of the risk–benefit assessment.

New approaches for preclinical safety assessment

Plasma-derived hepatitis B vaccine was introduced in 1981 on the basis of safety and immunogenicity studies in less than 800 individuals.[33] By contrast, the pneumococcal conjugate vaccine was licensed in the USA in 2000 on the basis of safety data for more than 60 000 children, and two rotavirus vaccines were licensed each with prelicensure safety data for more than 80 000 children.[25] This change in the licensure of new vaccines has had two effects: the first is an increase in the availability of safety information with which to decide whether to introduce new vaccines into widespread use, and the second is an increase in the cost of development and introduction of new vaccines, which has restricted the number of vaccines that a manufacturer can bring to market. A new vaccine costs about US$500 million to bring to market,[34] and therefore preclinical identification of vaccine candidates that might ultimately be hampered by safety concerns would be beneficial.

Several approaches have been used to predict vaccine safety. One approach has been to use bioinformatics to map potential vaccine antigens and relevant epitopes, and compare them with human proteins to avoid use of an antigen that might induce autoimmunity. This approach is especially useful for development of vaccines against infections that are known to be associated with autoimmune complications such as group A streptococcal infection.[35] However, protein homologies are many and are usually not associated with a risk of autoimmunity.[36] Such mimicry studies are of relevance to polysaccharide antigens that are known to mimic human cell-surface structures such as neural adhesin molecule.[37]

A second approach is to search for cross-reactive antibodies or T cells after vaccination in relevant animal models. Preclinical animal models can be used to search for specific biomarkers that can give an indication of the relative extent of non-specific cell activation after the use of new adjuvant formulations; this approach can now be done effectively with microarray technologies to identify gene-activation profiles in the first hours after vaccination[38,39] and through analysis of cellular phenotypes at the site of vaccine injection and in draining lymph nodes.[40] Analysis of cellular phenotypes in these lymph nodes is of particular importance to ensure that a vaccine formulation limits its immunostimulating effects to cells that present the relevant antigens to the draining lymph nodes and does not produce an overwhelming stimulation of the host immune system,[40] with the inherent risk of bystander enhancement of unwanted immune responses. However, enthusiasm for animal models has been tempered by differences between findings in such animal systems and those in human beings. Assessment of bacterial lipoprotein, a toll-like receptor 2 ligand, showed that it was associated with reduced immune-memory responses to pneumococcal antigens in human beings—a finding that animal studies did not predict.[41]

We have known for a long time that even vaccines associated with frequent adverse events, such as the old vaccinia vaccine, only induce severe adverse events in a few individuals.[42] Identification of specific genetic risk factors associated with adverse events has been difficult, although work continues in this area. If genetic risk factors are identified for specific adverse events, screening of individuals before vaccination and customisation of their vaccination regimen might be feasible in the future.

Systems biologists are developing computational models that will directly link phenotype to protein behaviour and gene regulatory networks.[43] As these models are refined, development will focus on those that are sufficiently accurate to predict the response of biological systems to perturbations, such as vaccines, and those that can define the perturbations of genetic regulatory networks, which will drive the system towards

improved immunogenicity without toxic effects. If these models are sufficiently detailed, vaccines could be engineered to drive the optimum immune response for a specific pathogen.

Hopefully, in the next decade, our understanding of the nature of the immune response and predictors of both safety and effectiveness will improve to the extent that development of new vaccines becomes more efficient both in terms of time needed to research and develop vaccines and selection of the most effective vaccine candidates. Overall, the challenge is to improve sensitivity and specificity of such assessments to ensure that safety issues are identified, while not rejecting vaccine candidates that could be safe and effective.

Post-licensure assessment of vaccine safety and effectiveness

In pre-licensure studies, specific risk groups, such as people with HIV infection or premature infants, are frequently excluded. If such exclusion occurs, safety and effectiveness of a vaccine should be assessed after licensure in the entire population for which the vaccine is recommended. Assessment can be accomplished through focused studies or through the use of large population studies. The availability of large computer databases containing clinical and vaccine-exposure information has revolutionised the assessment of safety and efficacy of vaccines after their introduction.[44] After the introduction and widespread use of a new vaccine, the assessment of its real-world safety profile and effectiveness is associated with several challenges. In almost all situations, such assessments do not occur within a blinded, randomised clinical trial. If a vaccine is routinely recommended, use of a placebo would usually be viewed as unethical. Hence, assessments are limited to observational studies; the absence of a true control group means that special care has to be taken to avoid bias. Historical controls are often considered, but coding systems, population characteristics, and the risk of possible confounders such as influenza outbreaks all change over time so that historical controls might not appropriately assess risk. People who refuse vaccination or those who are unvaccinated are usually quite different in their health-care seeking behaviour and hence might lead to underestimation or overestimation of the risk of adverse events.

One approach to assess real-world vaccine safety was suggested by Farrington and colleagues.[45] In their case series approach, the risk of an adverse event after vaccination was compared with the risk of the same event in the same individuals but in a time period outside the predefined risk window.

Generally, these approaches have been successfully applied to assess the safety of vaccines in large cohorts.[42] Pseudolikelihood statistical methods have been applied for rapid-cycle assessment of the safety of vaccines after introduction; the number of observed events is compared with the expected rate, usually at weekly intervals. This approach allows the identification of the presence or absence of adverse events within a brief period after vaccine introduction. When the combined measles, mumps, rubella, and varicella vaccine was introduced in the USA, this approach identified, within a few months, a higher risk of febrile seizures associated with this vaccine than with the combined measles, mumps, and rubella, and vaccinia vaccines given separately.[46]

Sometimes public health programmes require rapid introduction of new vaccines, which offers the opportunity to assess the safety of these vaccines in new populations, as was the case for the recent H1N1 influenza (swine flu) campaign.[47] Adjuvanted influenza vaccines were widely used and the vaccination of pregnant women with unadjuvanted and adjuvanted vaccines was expanded. From this campaign, we learned that the use of a properly prepared H1N1 influenza vaccine had a similar safety profile to that of seasonal influenza vaccine, and was not associated with an increased risk of Guillain-Barré syndrome, by contrast with studies of the 1976 vaccine.[48] Additionally, detailed knowledge of oil-in-water adjuvanted vaccines was gained from widespread use, confirming the safety that had been shown in previous studies.[49] Importantly, broad use of adjuvanted and unadjuvanted H1N1 influenza vaccines in pregnant women, because of the increased risk of sequelae due to influenza disease in this group, showed the feasibility of vaccinating this target population and the safety of these vaccines.[50]

Although focus is often on safety after the introduction of a new vaccine, assessment of vaccine effectiveness in a real-world setting or in a new population, such as in individuals infected with HIV, is also of interest. In the USA, the Centers for Disease Control and Prevention have implemented the Active Bacterial Core (ABC) surveillance network for the assessment of invasive bacterial disease due to pneumococcus, group A and group B streptococcus, meningococcus, and *H influenzae* type b.[51] After the introduction and routine use of the seven-valent pneumococcal conjugate vaccine in young children, this network was able to show not only the effectiveness of the vaccine in the target population but also a large reduction in disease morbidity and mortality in unvaccinated adults.[52] Similarly, this network was able to assess vaccine effectiveness in individuals infected with HIV.

Although we often assume that the effectiveness of a vaccine does not vary geographically, epidemiological characteristics of many diseases vary according to geographical location, nutritional status, and time. The serotype coverage of the seven-valent pneumococcal conjugate vaccine was higher than 85% when introduced in the USA, whereas coverage was lower than 50% in some countries in Asia;[53] thus, the observed effectiveness would also be different. For pneumococcus, colonisation occurs at a much younger age and is much more common in developing countries than in the USA or

Europe.[54] For this reason, introduction of the pneumococcal conjugate vaccine in South Africa has been accompanied by a sophisticated surveillance study of post-introduction effectiveness.

For many pathogens, the epidemiological characteristics of disease can change over time either in response to the introduction of vaccination or because of other factors.[55] Rotavirus vaccines, pneumococcal conjugate vaccines, meningococcal protein vaccines, human papillomavirus vaccines, and others developed in response to a specific epidemiological profile of antigens, genotypes, or serotypes causing disease will need sustained monitoring to assess any changes. For protein vaccines, monitoring of allelic variation and expression might be needed. If continuous surveillance shows that the antigenic profile has substantially changed, reformulation of the vaccine might be required. We have seen this reformulation happen with the development of ten-valent and 13-valent pneumococcal conjugate vaccines to replace the older seven-valent vaccine after the emergence of new serotypes; development of these vaccines took 10 years, and assessment of a prototype vaccine was required before licensure.[55]

Some organisms, such as *Helicobacter pylori,* are inherently more labile because of their non-clonal nature.[56] The ability of these organisms to change might outstrip the ability of our existing regulatory and development framework to make appropriate vaccines available. The existing framework was developed mainly for vaccines such as tetanus or *H influenzae* type b vaccines for which the antigens are largely invariant. Hence, rapid change of specific vaccine components was not needed. However, an adaptive approach might be prudent for vaccines against pneumococcus and perhaps even more so for protein-based vaccines such as meningococcus type B vaccine. A special development and regulatory approach has always been applied for influenza vaccines because of the inherent ability of the influenza virus to change almost continuously.[57] As we move into a period in which vaccines are developed for pathogens that have a high level of ability to adapt and circumvent vaccine protection, consideration of this model might be appropriate for other vaccines.

Advances in post-marketing assessment of safety and effectiveness in the past decade have emphasised the use of computerised clinical data systems and sophisticated disease-surveillance networks. Gathering genomic data could identify genetic subpopulations at risk of some adverse events. Such data will improve the comparative safety assessment of different vaccine formulations and adjuvants, and will represent a useful addition to the classic measurement of simple reactogenicity parameters, such as redness, swelling, and tenderness. The next decade promises to combine these advances with genomic and physiological studies to identify subpopulations at risk of adverse events or suboptimum vaccine responses.

Panel 2: **Challenges for the next decade**

- Application of new technologies to develop effective vaccines for diseases, which thus far have been resistant to vaccination, such as HIV infection, malaria, tuberculosis, cytomegalovirus, chlamydia, herpes simplex virus, and shigella
- Development of improved preclinical assessment of vaccine safety and effectiveness to speed development of new safer vaccines through translational medicine and systems biology approaches
- Development of a regulatory and manufacturing framework to allow adaptation of vaccines to changing pathogen characteristics; adaptation is done for influenza vaccines but might need to be done for vaccines against pathogens with intrinsic high antigenic variability, such as pneumococcal conjugate vaccines and new protein vaccines for pathogens such as meningococcus B
- Expansion of the pathogenic targets of vaccination beyond infectious diseases to include autoimmune diseases, chronic diseases of ageing, and cancer
- Development of age-appropriate combination vaccines for adolescents and adults
- Development and use of vaccines targeted at diseases in developing countries
- Expansion of global infrastructure for post-licensure vaccine assessment to include developing countries and vaccines (eg, malaria and tuberculosis vaccines) targeted at specific populations
- Development of prime-boost regimens to improve vaccine efficacy
- Use of innovative trial design to accelerate vaccine development
- Development of new adjuvants able to reverse T-cell anergy and thus be effective against chronic infectious diseases and cancer
- Improvement of public confidence in vaccines to increase vaccine acceptance and use

What is needed and what can we expect in the next decade?

Vaccines have progressed from the crude preparations used to prevent smallpox to one of the most technologically advanced and effective public health interventions devised by man. They have been used to largely prevent infectious diseases that are common globally. Targets for development of new or more effective vaccines include meningococcal B disease, respiratory syncytial virus infection, and lifestyle vaccines for HIV infection and other sexually transmitted diseases. Additionally, vaccines and vaccination strategies are needed to provide protection for very young infants, either through direct vaccination or through expanded vaccination programmes in pregnant women.

The frame of reference of vaccinologists should widen to address the needs of an ageing society, including the treatment and prevention of cancer, Alzheimer's disease, and perhaps some of the processes associated with the ageing process itself. Moreover, globalisation and the ease of international travel have made the threat of emerging infections more pressing. Rapidly emerging new infections will require development of new epidemiological, manufacturing, and regulatory processes.

The needs of low-income and middle-income countries are beginning to be addressed by vaccination programmes. Initially, programmes introduced wide use of existing vaccines, which were targeted at diseases prevalent in developed countries, such as the *H influenzae* type b or pneumococcal conjugate vaccines.[58] However, vaccines

that are in development or might be developed will target diseases specific to poorer countries, such as tuberculosis, typhoid fever, shigella, and malaria. These vaccines have the potential to address the huge economic toll on families, which often leads them into a downward spiral of chronic poverty.[59] Since many of these vaccines will be used largely in developing countries, the challenge will be to develop surveillance systems to ensure that their effectiveness and safety are monitored and are acceptable in these settings. In addition to expansion of target diseases for vaccination, the use of combination vaccines, which are common in infants, will probably expand to adolescents and adults to improve ease of administration and compliance.

The 21st century promises to be a fruitful one for the prevention and treatment of disease through vaccination, although challenges remain (panel 2). Efforts of many institutions, including the Hilleman Institute, the Novartis Vaccine Institute for Global Health, and the Bill & Melinda Gates Foundation, will probably lead to development and introduction of vaccines focused on the needs of developing countries. We have already seen an expansion of the target population for vaccines from children to adolescents.[60] With the world's population ageing, increased focus will be placed on new influenza, pneumococcal, and respiratory syncytial virus vaccines targeting this population. Additionally, the first therapeutic vaccine for prostate cancer has been licensed, ushering in a period of new therapeutic and preventive cancer vaccines.[61] However, as in the past, success will depend on our ability to successfully implement vaccination programmes that fulfil the potential of these approaches and programmes. Implementation will require development of appropriate infrastructure, improvement of public awareness about the benefits and risks of new vaccines in a way that encourages confidence in them, and creative thinking on the part of manufacturers and regulators to ensure that safe and effective vaccines are available in a timely manner.

Contributors

All authors contributed to the search for published reports, figure design, and writing of the report.

Conflicts of interest

RR is an employee of Novartis. SB is a consultant for Novartis. PHL has received honoraria from Novartis, GlaxoSmithKline, and Sanofi Pasteur, and is a consultant for Glycovaxyn, Wittycell, and DBV technologies.

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New Decade of Vaccines 3

Vaccine production, distribution, access, and uptake

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

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For human vaccines to be available on a global scale, complex production methods, meticulous quality control, and reliable distribution channels are needed to ensure that the products are potent and effective at the point of use. The technologies used to manufacture different types of vaccines can strongly affect vaccine cost, ease of industrial scale-up, stability, and, ultimately, worldwide availability. The complexity of manufacturing is compounded by the need for different formulations in different countries and age-groups. Reliable vaccine production in appropriate quantities and at affordable prices is the cornerstone of developing global vaccination policies. However, to ensure optimum access and uptake, strong partnerships are needed between private manufacturers, regulatory authorities, and national and international public health services. For vaccines whose supply is insufficient to meet demand, prioritisation of target groups can increase the effect of these vaccines. In this report, we draw from our experience of vaccine development and focus on influenza vaccines as an example to consider production, distribution, access, and other factors that affect vaccine uptake and population-level effectiveness.

Introduction

Licensed vaccines are available to prevent human infections caused by about 25 microbes. The actual number of vaccine products is, however, much higher because many combination vaccines and formulations are aimed at different age-groups and geographical regions, and both private and public markets. Although vaccines differ in effectiveness, as explained in the fourth paper in this Series,[1] most have contributed substantially to the improvements in human health across the past century. Among the large multinational pharmaceutical companies, only Sanofi Pasteur (part of the Sanofi-Aventis group) and GlaxoSmithKline manufacture a broad range of vaccines generally licensed for worldwide use. Others, such as Merck, Pfizer, and Novartis, offer a narrower range of products addressing particular disease indications or market niches.

This situation is changing with the growing number of manufacturers with headquarters in developing countries and the large new investment by multinational companies in vaccine research and development. As recently as 2005, only three of the present top ten pharmaceutical companies had substantial activities in vaccines. After recent mergers and acquisitions, the figure is now eight of the top ten. Vaccines are seen as an attractive and sustainable business for several reasons: vaccine demand has grown rapidly over the past decade and looks certain to grow further; many medical needs are unmet and vaccines do not exist for a range of important disease targets; innovative financing methods have greatly expanded markets, particularly in developing countries; advances in immunology and microbiology and our understanding of pathogenesis mean that previously intractable targets might now be within reach; and the vaccine sector has not been subject to the sharp revenue declines from expiry of patents that are plaguing much of the rest of the pharmaceuticals industry. Part of the reason for this last point is that vaccines are not as easy to produce and license generically as are small drug molecules, because it is the production processes as well as the products themselves that are licensed by regulatory authorities. Therefore, research and development, industrial know-how, and the associated costs provide high barriers to entry for potential new players, even for non-patented vaccines. Additionally, established manufacturers with a range of licensed antigens available are better able than small manufacturers to produce combination vaccines. Nevertheless, the drive for countries to be self-sufficient in production of essential vaccines, often with governmental support, has led to the expansion and technological advancement of several local

Key messages

- Manufacture of vaccines uses complex production methods, meticulous quality control, and reliable distribution channels
- Manufacturing technologies strongly affect vaccine cost, ease of industrial scale-up, stability, and, ultimately, worldwide availability
- Reliable vaccine production in appropriate quantities and at affordable prices is the cornerstone of developing global vaccination policies
- For vaccines with constrained supplies, such as influenza in a pandemic situation, prioritisation of target groups can increase vaccine protection
- As a result of strong growth, multinational pharmaceutical companies have recently returned to vaccine research and development with substantial investment
- Partnership organisations such as the GAVI Alliance have a powerful part to play in ensuring access to vaccines and future research and development
- New manufacturing technologies for influenza vaccine are being developed, but are likely to complement, rather than replace, egg-based production in the medium term

	Active component	Main manufacturing challenge
Oral polio vaccine	Three live attenuated viruses	Maintain phenotypic and genotypic stability of each of the three strains during production, and viability from blending through the supply cold chain
Rabies vaccine	Inactivated cell culture grown virus (eg, on Vero cells)	Ensure complete inactivation, but maintain immunogenic potency and avoid reactogenicity; achieve approprite biosafety level containment of live virus steps
Acellular pertussis vaccine	Purified proteins from *Bordetella pertussis*	Consistency of production and detoxification of components; maintain stability and quality control
Multivalent pneumococcal conjugate vaccines	Glycoconjugates of polysaccharides on a suitable carrier protein	Use of complex chemical conjugation chemistries tailored and done separately for each valency; yields; formulation to avoid immunological interferences between valencies; quality control of complex mixtures
Hepatitis B vaccine	Recombinant protein	Consistency of manufacturing, with reproducible immunogenicity and low contamination by host protein
Japanese encephalitis vaccine	Vectored vaccine	Need to show absence of potential for reversion or genetic rearrangement; robustness of process; freeze drying process and stability of product

Table 1: **Examples of vaccine classes and associated industrial challenges**

	Production method
Oral polio vaccine	Live attenuated virus grown in non-human cell culture (eg, primary monkey kidney culture or Vero cell line[3])
Tetanus vaccine	Tetanus toxin extracted from fermentations of *Clostridium tetani,*[4] inactivated with formaldehyde and adsorbed onto an adjuvant such as alum[4]
Measles vaccine (standalone and in MMR vaccine)	Live attenuated virus grown in cell culture of human diploid cells or chick embryo fibroblasts[5]
Influenza vaccine (intramuscular)	Influenza virus propagated in eggs, inactivated and further treated to give either split or subunit vaccines[6]
Diphtheria vaccine	Diphtheria toxin extracted from fermentations of *Corynebacterium diphtheriae*, inactivated with formalin and adsorbed onto alum adjuvant[7]
Whole-cell pertussis vaccine	Whole *Bordetella pertussis* grown in fermenters, heat killed, and inactivated with formalin[8]
BCG vaccine	Live attenuated *Mycobacterium bovis* produced in static surface culture[9]
Hepatitis B vaccine	Recombinant expression of HBsAg protein, as virus-like particles, in yeast species[10]
Haemophilus influenzae type b vaccine	Polysaccharide purified from culture of *Haemophilus influenzae* and conjugated to a carrier protein such as inactivated tetanus toxoid, diphtheria toxoid, tetanospasmin, mutant diphtheria protein, or the outer membrane vesicle protein of *Neisseria meningitidis* serogroup B[11]
MMR vaccine	Live attenuated virus grown in chick embryo fibroblast culture for mumps vaccine;[12] live attenuated virus grown in human diploid fibroblast culture for rubella vaccine[13]

The production methods listed might not be exhaustive for each antigen type. MMR=measles, mumps, and rubella.

Table 2: **Production systems for the top ten human vaccine antigens by doses produced**

producers. These producers have achieved WHO prequalification to assure a consistent standard of quality, safety, and efficacy of medicinal products,[2] and have built sufficient capacity to supply markets in developing countries at competitive prices, either directly or via organisations such as UNICEF and the GAVI Alliance.[1]

Vaccine production by major suppliers

A wide range of technologies participate in manufacture of a comprehensive portfolio of vaccines. Table 1 provides examples of the main vaccine types and identifies associated industrial and technical challenges. Technologies are needed not only for bulk production but also for vaccine formulation and stabilisation, addition of adjuvants, design of delivery devices, and to provide the capacity and logistics for worldwide supply and distribution.

The production method used for a particular vaccine can greatly affect manufacturing capacity and cost of goods and, hence, availability (table 2). For example, the oral polio vaccine Sabin strains grow well in culture to titres in excess of 10^8 plaque-forming units (pfu) per mL and are used at a dose of about 10^5–10^6 pfu per mL in human beings.[14] Preparation of the live attenuated oral polio vaccine can be achieved at high capacity, albeit with complex and lengthy quality control, with hundreds of millions of doses produced at a low cost, making possible the national immunisation days that have been the driver of WHO's poliomyelitis eradication programmes.[15] By contrast, complex vaccines—such as multivalent glycoconjugates for pneumococcus[16] or meningococcus,[17] the multivalent virus-like particles for human papillomavirus,[18] and purified multicomponents of acellular pertussis vaccines[19]—can have substantially lower yields of individual components, a less robust production process (leading to batch production failure), and lengthier and more expensive quality control, requiring much more investment in resources and facilities, resulting in substantially lower global capacities and higher cost of goods.

Vaccine production includes a high level of quality control at every stage of the process and compliance in a wide range of assays is essential for batch release. Assays include precise definition of physicochemical properties such as pH and osmolality, component identity and stability analyses for antigens, excipients, and adjuvants, microbiological testing for sterility, concentration and potency testing, and animal-based testing for toxic effects. The testing process for a vaccine can be further complicated by different regulatory agencies using different release criteria and requiring different testing methods for release in their specific jurisdiction. Thus, the quality control test profile is specific to each vaccine and to each country of release. For example, quality control testing for diphtheria toxoid vaccine bulk includes all essential assays plus animal testing for at least 6 weeks to show absence of residual toxicity. However, diphtheria toxoid is routinely used in combination vaccines, such as the diphtheria, tetanus, and acellular pertussis vaccine, and therefore a further series of quality control tests have to be done after blending of the additional antigens. The manufacturer again has to show sterility, that the physicochemical properties are correct and stable and that all components in the combination are identifiable and at the correct concentration and potency. Further testing of residual toxic effects in animals has to be done at this stage, adding at least a further 6 weeks to the release time.

Complexity in the worldwide supply of vaccines is caused by variations in the manufacture of different vaccines, including batch size, quality control release tests, shelf life, filling into single-dose or multidose vials or syringes, production of freeze dried or stabilised liquid formulation, cold-chain requirements, and packaging and labelling in different languages for different markets. For example, Sanofi Pasteur manufactures two versions of the inactivated polio vaccine, but the main difference between the versions is the cell substrate on which they are grown (MRC-5 cells *vs* Vero cells), leading to two specific and different licensed production processes. These two inactivated polio vaccines are included in 16 different standalone or combination vaccine formulations, which are dispensed into 32 different filled products, packaged into 64 presentations, and, when boxed and labelled according to requirements of specific country markets, result in more than 300 different final products being distributed across the world. Furthermore, products licensed in, and destined for, one particular market cannot usually be diverted to another in response to fluctuations in demand or problems with shipments or inventory control. Organised distribution of vaccine products is therefore a crucial part of the overall supply chain to ensure vaccines eventually reach their target.

Inevitably the complexities in manufacturing lead to occasional disruption of supply caused by, for example, batch or production failure, quality control issues with bulk or finished products, breakdown of the cold chain in delivery, and failure to predict variations in demand. However, for the most part, such disruptions are not a serious long-term impediment to vaccine access. The remedy to short-term supply interruptions is to develop and formulate vaccines with a long shelf life so that inventories can be established to anticipate occasional delivery failure. Manufacturers also benefit from individual countries and organisations (eg, UNICEF) making long-term procurement arrangements on the basis of accurate demand forecasting and budgeting across several years. With reasonable assurances or guarantees of purchase, the industry can confidently make the investments needed to ensure long-term supply and be prepared to deal with occasional fluctuations in demand, while maintaining fair pricing policies.

Distribution and supply

Distribution and supply is dependent on licensure of vaccines in particular national markets. Vaccines can be licensed directly in countries with highly developed regulatory authorities, whereas other countries rely on licensure in the country of manufacture, followed by review and approval in the final country of use. In all cases, licensing includes approval of the manufacturing process and facilities, and some countries also require inspections. For procurement of vaccines by UN agencies, products need WHO prequalification to assure a consistent standard of quality for countries with poorly developed regulatory agencies.[20] Prequalification is reliant on the vaccine having been previously licensed in the country of manufacture by an authority that is regarded as functional by WHO. Additionally, for vaccines that are manufactured but not used in the country of origin, mechanisms exist, such as the Article 58 regulation in the European Union (EU)[21] and rapid review by the US Food and Drug Administration under the investigational new drug process, to expedite availability of new vaccines that address a primary medical need in emerging nations.

Therefore, the complex production and product range, licensure, and methods of distribution are country dependent and affected by national vaccination policies. In the USA, for example, access to vaccines is usually via a physician who orders directly from a manufacturer or distributor (Sanofi Pasteur operate a direct-to-physician policy with dispatch within 24 h of ordering). Vaccines can be advertised directly to the customer through the media, and the influenza vaccine is widely available to the public from a range of retail outlets where immunisation by a professional can be directly purchased. In the EU, member states have varying distribution policies, but typically manufacturers ship to distribution centres and wholesalers. In some EU countries, price controls are imposed by government and vaccines are procured by government tender (Italy, France, and the UK), whereas in other countries, sales are predominantly to the private market where price control and bulk

purchasing are reduced (eg, Germany). These buying models determine how manufacturers supply vaccines to each country. Publicity and advocacy typically target both the consumer (eg, via wellbeing clinics and primary care centres) and medical professionals, especially paediatricians and general practitioners.

Other countries can be supplied after direct orders from public health departments, sometimes private customers on a case-by-case basis, or international non-governmental organisations. Public markets are usually served by tenders, where international manufacturers compete with each other and with local suppliers on price, volume, and, importantly, reliability of supply. For developing countries that qualify for support from the GAVI Alliance,[22] the advantages of bulk purchasing are provided by long-term agreements negotiated by organisations such as UNICEF. The model for these agreements was provided by the Pan American Health Organization, which established the revolving fund for vaccine procurement in 1979. The purpose of the fund was to provide participating member states with a means to assure the smooth and constant flow of high-quality vaccines, syringes, and cold-chain equipment at affordable prices, initially for the implementation of immunisation programmes in Latin America and the Caribbean.[23]

Vaccines vary in stability and, thus, shelf life in their final container. An essential part of the supply process is maintenance of a cold chain that is robust, reliable, and routinely monitored for possible deviations between the manufacturer and end user.

Access and uptake

In almost all countries, a primary series of vaccination of infants is well established and the vaccines included are readily available. Although the precise vaccines and schedules vary between countries, programmes regularly include vaccination against diphtheria, tetanus, and pertussis (DTP vaccine), measles, poliomyelitis (inactivated or oral vaccine), and, dependent on the geographical region, hepatitis B, *Haemophilus influenzae* type b infection, and tuberculosis (BCG vaccine). In some countries, the BCG, oral polio, and hepatitis B vaccines are given at birth, and the remaining vaccines are typically given in a three-dose schedule from 6 weeks to 6 months of age, with fourth and sometimes fifth booster doses given in the second year of life and before school, but this practice varies between countries. In the past decade, pneumococcal conjugate vaccines (initially seven-valent formulations and subsequently ten-valent and 13-valent formulations) and, in some countries, the rotavirus vaccine have been added to the vaccination schedule from 6 weeks to 6 months of age. Hepatitis A vaccine can also be given to children at as early as 1 year of age. The live attenuated measles vaccine is given subsequently, typically at about 12–15 months of age, to avoid the effect of maternally acquired antibodies. In most developed countries, measles vaccination is provided as part of a trivalent formulation that includes live attenuated mumps and rubella vaccines or even a tetravalent formulation with added varicella. Usually vaccination is a single dose followed by a preschool booster. Thus, through infancy, most children acquire immunity through vaccination to diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, measles, and, in some countries, mumps, rubella, pneumococcal infection, rotavirus infection, varicella, tuberculosis, *H influenzae* type b infection, and hepatitis A. Vaccination campaigns against specific pathogens, such as cholera, typhoid, or influenza, can extend this list.[24–26]

Differences in vaccine use between developed and low-income countries mainly relate to the combination vaccines licensed and the type of a specific vaccine. For example, whole-cell pertussis vaccine is easier to manufacture and has a lower cost of goods than do the multicomponent acellular pertussis vaccines preferred by developed countries. Hence developing countries tend to use the DTP vaccine with whole-cell rather than acellular pertussis. For reasons of cost and vaccine availability, many developing countries also use the measles standalone vaccine rather than combined vaccines including protection against mumps, rubella, and varicella, and the oral rather than the inactivated polio vaccine.

For more on the **revolving fund for vaccine procurement** see http://www.paho.org/english/hvp/hvi/revol_fund.htm

Particularly in developed countries, vaccines have been developed for adolescent populations, with specific formulations of the DTP vaccine and combined DTP and inactivated polio vaccines to boost childhood-acquired immunity. These boosters are regarded as important to provide herd immunity, particularly to pertussis.[27] Other adolescent vaccines available include the human papillomavirus vaccine[28] for protection against cervical cancer (Cervarix, GlaxoSmithKline, Rixensart, Belgium) or cervical cancer plus genital warts (Gardasil, Sanofi Pasteur, Lyon, France), and several meningococcal meningitis vaccines that can be either polysaccharide or glycoconjugate based and monovalent, bivalent, or tetravalent. However, the threat of infection in adolescents also includes hepatitis C virus, *Neisseria gonorrhoeae* (gonorrhoea), *Treponema pallidum* (syphilis), *Chlamydia trachomatis* (chlamydia), Epstein-Barr virus, herpes simplex virus type 2, cytomegalovirus, and HIV, against which we do not have licensed vaccines. A range of vaccines are also available for specific geographical or environmental risks, including rabies, Japanese encephalitis, tick-borne encephalitis, yellow fever, typhoid, and cholera.

In developing countries, access to and uptake of vaccines have been hugely improved in the past decade by the launch of the GAVI Alliance, which aims to save children's lives and protect people's health by increasing access to immunisation in poor countries. The 72 countries that can apply for support from the GAVI Alliance are home to about half the world's population.[29]

The GAVI Alliance estimates that between 2000 and 2009, more than 257 million children were immunised with vaccines funded by the GAVI Alliance, and by the end of 2009, more than 5 million future deaths had been prevented through routine immunisation against hepatitis B, *H influenzae* type b infection, and pertussis and one-off investments in immunisation against measles, poliomyelitis, and yellow fever.[1,30] In these 72 countries, immunisation coverage has climbed steadily and about 80% of children now receive three doses of DTP vaccine.[30] For the basic vaccines in the Expanded Programme on Immunization (EPI), global manufacturing capacity is adequate. Thus, incomplete coverage with these traditional vaccines is mainly a result of the need for better delivery infrastructure.[31]

By contrast with the EPI vaccines, availability of new and more complex vaccines in developing countries lags substantially behind that in wealthier countries. This situation is partly caused by manufacturing capacities that are seldom sufficient to satisfy global demand in the early years of licensure, and is partly due to the economic reality that companies need to recoup research and development investment (which can be in the region of US$1 billion for a new vaccine) by prioritisation of supply to markets that can sustain a high price. In the absence of specific purchasing and supply agreements, new vaccines are often unavailable or unaffordable for many countries for extended periods. As a result, for the 2008 global birth cohort of about 129 million children, the GAVI Alliance estimates that 34% of children did not receive the hepatitis B vaccine, 71% did not receive the *H influenzae* type b vaccine, 92% did not receive the rotavirus vaccine, and 93% did not receive the pneumococcal conjugate vaccines.[32] Major funders, such as the GAVI Alliance, donor countries, the Bill & Melinda Gates Foundation, and international organisations, have recognised this challenge and have designed innovative financing schemes and other measures to accelerate introduction and to support the purchase of new vaccines for developing countries.[1,33] The GAVI Alliance is also undertaking efforts to strengthen and fund health systems to overcome barriers to vaccine delivery.[34]

In view of the continuing cholera epidemic in Haiti, the supply of cholera vaccine merits special mention. Although three vaccines are approved for cholera in individual countries, only one (Dukoral, Crucell, Stockholm, Sweden) has been prequalified by WHO.[35] For the other two vaccines, only an estimated 400 000 doses are available worldwide for shipping from manufacturers,[36] which is far from adequate for the Haitian population of about 10 million who each need two or three doses of each vaccine for immunisation. As several groups have argued, a global stockpile of cholera vaccines is needed to respond to emergencies, such as that in Haiti, because routine demand has not ensured adequate supplies for such a surge in need.[36,37]

The effort to provide adequate and timely supplies of pandemic influenza vaccines—either in advance, for the possible pandemic of influenza A H5N1 that has raised concerns in the past decade,[38] or as a pandemic emerges, as in the case of swine influenza A H1N1 in 2009[39]—provides a different example of the economic and scientific challenges of vaccine supply and access that affect both developing and developed countries, though to different extents. In a case study of influenza, we discuss influenza manufacture and the opportunities to use new methods of production, and how vaccine access might be managed to achieve maximum protection.

Production and supply of influenza vaccine

Seasonal influenza vaccine

As discussed in the first paper in this Series,[40] influenza viruses continuously undergo antigenic drift, resulting in the need to routinely monitor circulating strains and update the annual influenza vaccine formulation. Monitoring of human influenza is a truly global effort: a network of over 120 national influenza centres in more than 90 countries[41,42] work with sentinel medical professionals to gather clinical swabs for virus isolation. The clinical isolates are supplied to the four WHO collaborating centres, located in Atlanta (GA, USA), Tokyo (Japan), Melbourne (VIC, Australia), and London (UK), for antigenic and genetic analysis to assist WHO in preparing the two annual influenza strains recommendations: in February, for manufacturers to produce the northern hemisphere vaccine to be used from September onwards of the same year; and in September, for manufacturers to produce the southern hemisphere vaccine to be used from March onwards of the following year.

The timing of vaccine production and release is a crucial factor, especially in the northern hemisphere because capacity is typically more constrained, relative to demand, than in the southern hemisphere. About 400 million doses are manufactured, formulated, filled, packaged, and released in the autumn, which is a substantial logistical challenge. Producers routinely try to get a head start by starting manufacture "at risk" in January with the vaccine seed strain judged most likely to be retained from the previous year. The remaining two bulks of monovalent vaccine are then manufactured as the WHO-recommended vaccine seed strains become available. Large multinational companies manufacture bulk vaccine for about 180 days, of which potentially 60 days are "at risk".

The point at which manufacturers can start the final production steps, formulation and filling, is not within their own control, but is dependent on the availability of specific antisera for use in the regulatory-approved potency and release assay—single radial immunodiffusion. Antisera are prepared, calibrated, and distributed by the National Institute for Biological Sciences and Control in the UK, the Center for Biologics

Evaluation and Research in the USA, the Therapeutic Goods Administration in Australia, and the National Institute of Infectious Diseases in Japan. Receipt in late May allows formulation and filling of the vaccine batches to start and then run concurrently with production of the final monovalent bulk. Final product release follows different routes dependent on specific regulatory requirements, but submission of a variation to the licensed process can lead to accelerated approval by regulators. In the USA, the master seed lots are checked for antigenic similarity to the WHO-recommended strains, and then five monovalent batches of each strain and all trivalent batches are tested for antigenicity and released. The final packaged product has no formal release process and typically the first vaccine doses begin to ship to customers in mid-July. In Europe, the master seed lots are not assessed in the same way but there is a regulatory requirement for an annual clinical trial to assess safety and immunogenicity.[43] Each component has to fulfil established immunogenicity endpoints before the vaccine is approved for distribution and sale. This process adds risk for the manufacturers because by the time the clinical results become available, nearly all the doses have been manufactured and the formulation and filling campaigns are well underway. The seasonal clinical trial affects timing, especially because the trial cannot normally begin until reagents for single radial immunodiffusion are available to allow correct formulation of the clinical trial batches. Consequently, vaccine doses are not usually ready for shipment in Europe until mid-August, about 4 weeks later than in the USA.

Pandemic influenza vaccine

The egg-based manufacturing system has been reliably supplying influenza vaccine for several decades. However, this system has clear timing and capacity constraints and, following the influenza H1N1 pandemic in 2009, a perception has arisen that it needs to be updated. The virus could be grown in cell cultures such as MDCK,[44] Vero,[45] or PER.C6,[46] or recombinant DNA technology could be used to express haemagglutinin and potentially other viral proteins in, for example, insect cells (Protein Sciences,[47] Novovax[48]), tobacco plants (GreenVax,[49] Medicago[50,51]), or the fungus *Neurospora crassa* (Neugenesis[51]). Such technologies are potentially better able to respond to global demand in a pandemic because of more rapid production and greater surge capacity than in egg-based manufacturing. But which of these options can bring benefits while performing as reliably as the existing system? Several criteria should be used to assess the response of new technologies to seasonal and pandemic demand (panel).

Economic factors also affect the choice of replacement technology, especially considering the already substantial investment in egg-based production that has been made globally by producers. First, the research and development cost of a new influenza vaccine will be high because the novel approaches will probably need full clinical development, potentially including large efficacy studies across several years. The cost from the research idea to product launch is likely to be several €100 million plus the cost of new production facilities. Second, growth of the market for influenza vaccination has led to investments that have increased global capacity for seasonal influenza vaccine to about 600 million doses for the northern hemisphere. Capacity is expected to increase to about 1 billion doses by 2018. However, market demand is not expected to increase at the same rate, potentially leading to an excess supply. This situation will lead to further pressure on pricing and reduce return on investment, thereby reducing incentives for investment in new technologies.

For manufacturers to justify the replacement of existing production technology from an economic point of view, any new technology will need to deliver within the required regulatory and supply environment, and also offer substantial advantages over egg-based manufacturing. Among the new systems under assessment, at this stage none clearly has all the characteristics needed to fundamentally alter manufacturing. In 2013, when the first large-scale cell culture facility is due to start market supply, production capacity for the northern hemisphere is expected to be about 750–800 million doses per year, of which about 74 million doses are planned to be from cell culture and the remainder (about 90% of world production) will be from egg-based production. Although the switch to alternative technologies is likely to gather momentum, the timescales needed to license new production systems, secure capital investment, and develop infrastructure for manufacturing will mean that egg-based manufacture of influenza vaccines will be used for some time to come.

Capacity for seasonal influenza vaccine is expected to exceed global demand, but in the event of a pandemic, substantial further capacity is needed very quickly. From a commercial perspective, investment in further capacity is not easy to justify without a concomitant annual market expansion to use all of the supply. Therefore alternative approaches to expand influenza vaccine supply in a pandemic need to be considered. One such approach is dose sparing provided by addition of adjuvants. During the swine influenza H1N1 pandemic in 2009, Novartis released a vaccine containing 7·5 µg of antigen adjuvanted with MF59[52] and GlaxoSmithKline released a vaccine with 3·75 µg of antigen adjuvanted with AS03 (the unadjuvanted dose is 15 µg).[53] This process allows an increase in vaccine supply from the same industrial base, assuming that supply of the adjuvant is not restricted. By contrast, the use of adjuvants in seasonal influenza vaccines is much debated and the need for adjuvants is less obvious, certainly from a dose-sparing perspective.

Panel: **Criteria for assessment of new technologies for pandemic and seasonal influenza**

Time to availability of the first doses
The speed of the industry response from receipt of the WHO-recommended strains to release of the first fully controlled and formulated batch is crucial for the pandemic response.

Time to availability of the last doses
The success of a campaign is determined by how quickly all doses can be supplied. Most manufacturers release their initial batches within days of each other, but their different logistics and capacities mean that their overall contributions to global supply are very different.

Scalability
Any new manufacturing system needs to be readily scalable to the large production volumes needed for global supply. Appropriate scale-up is not established for most of the technologies that could potentially replace egg-based production. Moreover, manufacturing needs to be efficient to keep cost of goods to a minimum, and rapid formulation and filling on the appropriate scale are an essential part of this process.

Regulatory aspects
Any new technology needs to be robust and applicable to all influenza types, subtypes, and strains, in a way that allows approval by regulators via variations to the licensed process, on time and with the lowest possible risk.

Surge capacity
The ability to quickly scale and deliver a substantial increase in production from that used for routine seasonal vaccination is quite difficult to build into an industrial system. Generally, capacity is sized and built on routine demand, and manufacturers cannot afford to build facilities for an event that might occur only three or four times per century. The notion of a warm-base facility funded in partnership with government and ready for use in case of a pandemic has been much discussed and is a laudable goal. However, the logistics are not straightforward. Highly trained staff would need to be permanently available to manage and maintain the facility. Moreover, sufficient raw materials to meet surge requirements would need to be available at short notice.

Flexible manufacturing platform
A technology with reduced time to final dose would shorten the total time needed for manufacturing. Thus, the facility could be used to make other products if the production system is flexible enough and constructed in a way relevant to other vaccines or biologicals, which would reduce cost of goods.

Dispersed manufacturing capability
During the 2009 influenza H1N1 pandemic, the need for national self-sufficiency was discussed extensively, especially by countries which noted inequality in the distribution of pandemic vaccine. Thus, a further criterion is how adaptable the new technologies are to distributed production.

Development of pandemic vaccines for emergency use also requires some flexibility in the regulatory pathway because time is not sufficient for full clinical development. For Europe, the European Medicines Agency has developed a guideline[54] to allow rapid market authorisation of a variation of a vaccine against a reference virus via an application containing only the new production data for a vaccine against a potentially pandemic strain. The eventual pandemic vaccine would have to be produced in the same way, including formulation and addition of adjuvants. This process was used during the swine influenza H1N1 outbreak to release pandemic vaccines in the EU.

Principles for allocation of restricted supplies of vaccines

The quantity of vaccines available and affordable for many countries is often less than that needed to cover the entire population. As the 2009 pandemic of influenza H1N1 showed, existing technology cannot be used to scale up production of vaccine fast enough to immunise even populations of the wealthiest countries in the timeframe needed to ensure protection. In this type of situation, vaccine use should be prioritised to achieve the greatest benefit for public health. A major problem at present is that the most potent force in prioritisation of pandemic influenza vaccination is the market: through advance contract commitments, wealthy countries had a claim on virtually the entire available supply in the 2009 pandemic.[55–57]

In jurisdictions that do have access to vaccines for pandemic influenza, theoretical models provide some principles for allocation of restricted supplies that will best achieve various public health objectives.[58,59] Vaccines serve two related but distinct functions: to protect vaccinated people against infection and severe disease; and to reduce transmission, thereby offering indirect protection to those not vaccinated via herd immunity. With few vaccines available, a fundamental question for allocation is how to balance these goals. Vaccines most effectively reduce transmission if they are given to the groups that are most likely to be infected and most likely to transmit the infection onward,[58] which in practice often means children. However, the groups most likely to get severe disease if they are not vaccinated can be a very different group, specifically adults and people with certain predisposing disorders.[59] Therefore, achievement of one of these goals typically comes at the expense of the other.

Models have shown that vaccination of transmission groups is most likely to be effective when large quantities of vaccine are available early in the epidemic.[59] By contrast, direct immunisation of individuals at highest risk will probably be best when vaccine supplies are small or arrive late because such vaccination programmes can only make a slight dent in transmission, hence the protection offered to unvaccinated individuals is small,[59] and the core transmission groups, such as children, tend to become less important to transmission as the epidemic progresses, because many of them are already immune.[58] One caveat should be noted, however: many individuals who are at high risk of severe outcome, such as elderly or immunocompromised people, might have suboptimal immune responses to the vaccine.[60] Even in seasonal influenza, vaccination of elderly people is not totally effective.[60] The decision to target vaccination at high-risk groups should ideally be based on evidence that the vaccine is effective in these

groups, which is difficult to obtain in the urgent setting of a pandemic.

With existing technology, vaccine supply is likely to be restricted and delayed relative to the spread of an influenza pandemic; the timescale of present vaccine manufacturing is simply slower than the timescale in which influenza spreads. However, consideration of how vaccines can be used to reduce spread of influenza is worthwhile because this goal is achievable for seasonal (non-pandemic) influenza, and an understanding of this approach can help to define what would be needed from an increased capacity to manufacture pandemic vaccine. Theoretical models provide some basic principles, but, as always, these principles need to be interpreted in view of available data because they do not apply uniformly to all settings.

First, growth of an epidemic can be substantially reduced or even stopped by vaccination of less than the entire population.[61] Epidemics grow when, on average, each infectious person infects more than one additional person.[61] In the early phase of past influenza pandemics, the number of secondary cases per infected case—the reproductive number (R)—was estimated to be 1·3–1·8 for 2009[62–65] and 1·8–2·0 for 1918,[66,67] but was possibly even higher in the spring of 1918.[68] In seasonal influenza, the reproductive number is much lower because a proportion of the population has partial immunity. Immunisation can slow the spread of infection by reducing the reproductive number, and can essentially halt spread by bringing the number below one.[61] If immunisation occurs at random, the proportion of people who need to be vaccinated to halt transmission is about:

$$p_c \approx \frac{R-1}{Rf}$$

where f is the efficacy of the vaccine.[61] For a vaccine of 90% efficacy and a reproductive number of five, vaccine coverage of about 89% would be needed to halt transmission.[61] This estimate is merely illustrative and can be improved by detailed simulation or analytical models,[69–72] but in all situations, coverage need not be 100%.

Second, other interventions, such as reduction in contact and use of antiviral prophylaxis and treatment, can reduce transmission by working in concert with vaccination and allowing major reductions in the epidemic growth rate with less coverage than would otherwise be needed.[69,71] Last, the benefits of vaccination can be maximised by identification of the groups that are most crucial to transmission.[58] One approach is to identify in advance the most likely core transmission groups on the basis of behavioural data[73] or other information about contact patterns; these data can then be used to predict the relative reduction in transmission from vaccination of various groups.[74] If these data are not available, patterns of disease incidence and immunity in the population can be used to estimate, with certain assumptions, which groups should be vaccinated.[58] All such methods suggest that for seasonal and pandemic influenza, the greatest reduction in transmission would be achieved by vaccination of school children, a conclusion that is consistent with data from observational studies[75] and a randomised trial.[76] Such strategies are particularly appealing for seasonal influenza, for which vaccine is generally available early, in view of concerns about the direct benefits of vaccination of elderly people[63] who suffer the vast majority of severe morbidity and mortality in seasonal influenza.[77,78] Indeed, the USA has recently recommended near-universal seasonal influenza vaccination.

	Challenge	Potential effect and options for improvement
Anti-vaccine propaganda	Counteract misleading and false messages that discourage uptake of safe vaccines	Improve public health messaging and advocacy
Crowded immunisation schedule	Introduction of new childhood vaccines	Develop new manufacturing and blending technologies to ease development of vaccine combinations
Improvement of global vaccine infrastructure	Maintain vaccine quality while driving down costs; strengthen national regulatory authorities in developing countries	Increase development of vaccines with primary launch in developing countries; harmonise regulatory and quality requirements to allow simplified and simultaneous licensure worldwide
Influenza vaccine uptake	Increase protection against influenza by increasing global uptake; expand industrial base and diversify production technologies in a commodity vaccine market	Expand seasonal demand through strengthened advocacy to increase available capacity for a pandemic response; drive establishment and achievement of national recommendations for influenza vaccination
Equity and timeliness of global vaccine access	Ensure access to new vaccines in developed and developing countries simultaneously	Secure advanced market commitments, external funding, and other mechanisms
Breadth of vaccine coverage	Develop vaccines that are effective against a wide range of antigenic variants (eg, universal influenza vaccines[79])	Increase valency of multivalent vaccines; develop vaccines against conserved antigens, including sets of conserved antigens; possibly, improve adjuvants[80]
Production and updating of estimates of vaccine effectiveness outside of phase 3 trials	Measure the effect of vaccine introduction on morbidity and mortality in settings where no clinical trial was done or with evolution of the pathogenic population[81]	Improve surveillance for disease outcomes and intermediates (eg, carriage) in developing countries where vaccine is introduced;[82] maintain surveillance where it already exists to assess long-term effects of vaccine

Table 3: **Major issues for the next decade and beyond on vaccine production, distribution, access, and uptake**

Conclusions and perspectives

Capacity for global manufacturing of vaccines has substantially improved in the past decade and looks set to continue to do so because investment in research and development and industrial production methods is rapidly increasing. These improvements have led to increased access to vaccines in many nations, resulting in high population coverage with established vaccines and positive initiatives to introduce new vaccines as they are developed and launched. Non-governmental organisations, such as the GAVI Alliance, continue to play an extremely important part, especially for the developing world, via policies on advocacy, creative financing to provide incentives to manufacturers, and procurement strategies. However, several new and underused vaccines have the potential to save many lives if they can be delivered to populations at risk. This objective, together with the research and development challenges associated with pathogens that are difficult to develop vaccines against, as described in the first paper of this Series,[40] sets the agenda for the next decade (table 3).

The threat of pandemic influenza is ever present and occurrence of the 2009 influenza H1N1 pandemic in no way reduces the risk of a more virulent pandemic arising at any time. Unfortunately, the response of global industry is not yet sufficient to meet the full need for pandemic vaccine in a timely and equitable manner and, even with improvements, vaccine will need to be used wisely to achieve maximum protection. We have described the challenges to improvement of pandemic vaccine supply and the principles to optimise use of restricted supplies in the meantime. This problem has other possible technical solutions, including development of influenza vaccines that provide broad protection across subtypes and could be manufactured in advance. Recent progress on this front, although still preclinical, warrants further investigation.[83–87]

In the past decade, expanded markets, realistic pricing, improved advocacy, and wise health priorities have attracted substantial new investment into the industry, generating a so-called vaccine renaissance.[88] Although much work is ahead, the next decade of vaccines is well placed to maintain this momentum and to allow the full benefit of vaccination to be felt by all the world's population.

Contributors

All authors contributed to the writing and editing of the report.

Conflicts of interest

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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.

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

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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

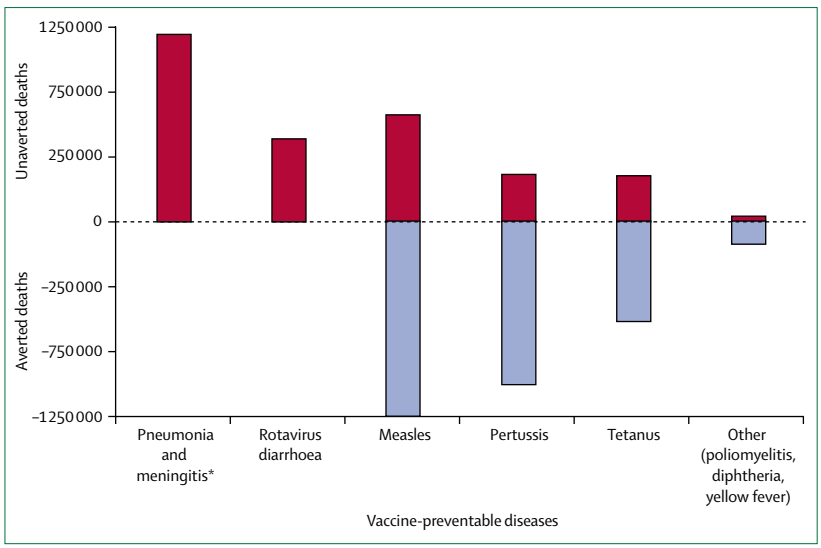

Figure 1: **Global annual estimates of deaths averted and still happening from vaccine-preventable diseases in children younger than 5 years, 2000–04**
Data are taken from Watt,[1] O'Brien,[2] Parashar,[3] Brenzel,[4] and colleagues. *Vaccine-preventable component caused by *Streptococcus pneumoniae*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

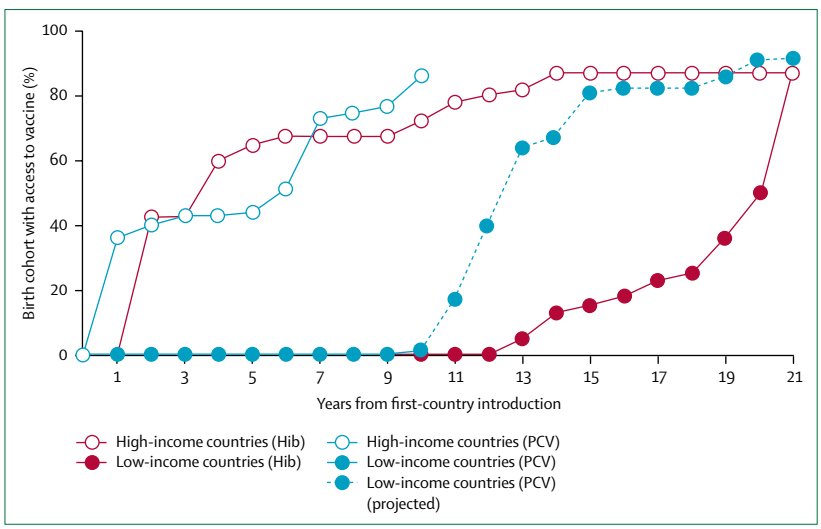

Figure 3: **Uptake of Hib and pneumococcal vaccines in high-income versus low-income countries**
Hib=*Haemophilus influenzae* type b. PCV=pneumococcal vaccine. Dashed line=projected uptake. Solid line=actual uptake.

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,

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

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

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New Decade of Vaccines 5

Addressing the vaccine confidence gap

Heidi J Larson, Louis Z Cooper, Juhani Eskola, Samuel L Katz, Scott Ratzan

Vaccines—often lauded as one of the greatest public health interventions—are losing public confidence. Some vaccine experts have referred to this decline in confidence as a crisis. We discuss some of the characteristics of the changing global environment that are contributing to increased public questioning of vaccines, and outline some of the specific determinants of public trust. Public decision making related to vaccine acceptance is neither driven by scientific nor economic evidence alone, but is also driven by a mix of psychological, sociocultural, and political factors, all of which need to be understood and taken into account by policy and other decision makers. Public trust in vaccines is highly variable and building trust depends on understanding perceptions of vaccines and vaccine risks, historical experiences, religious or political affiliations, and socioeconomic status. Although provision of accurate, scientifically based evidence on the risk–benefit ratios of vaccines is crucial, it is not enough to redress the gap between current levels of public confidence in vaccines and levels of trust needed to ensure adequate and sustained vaccine coverage. We call for more research not just on individual determinants of public trust, but on what mix of factors are most likely to sustain public trust. The vaccine community demands rigorous evidence on vaccine efficacy and safety and technical and operational feasibility when introducing a new vaccine, but has been negligent in demanding equally rigorous research to understand the psychological, social, and political factors that affect public trust in vaccines.

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

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Introduction

Tremendous progress has been made in the development of new vaccines, along with increasing access to new and underused vaccines in the lowest income countries. But, vaccines—often lauded as one of the greatest public health interventions—are losing public confidence. Some vaccine experts describe the problem as a "crisis of public confidence"[1] and a "vaccination backlash".[2]

Public concerns about vaccine safety and vaccine legislation are as old as vaccines themselves—dating back to the anticompulsory vaccination league against mandated smallpox vaccination in the mid-1800s.[3,4] Some common concerns shared by the antivaccination groups of the 1800s and those of today are related primarily to arguments against mandated vaccination, or imposed vaccine schedules. But current antivaccination groups have new levels of global reach and influence, empowered by the internet[5] and social networking capacities allowing like minds to rapidly self-organise transnationally, whether for or against vaccines.[6] These groups reach people who are not necessarily against vaccines, but who are seeking answers to questions about vaccine safety, vaccine schedules, changing policies, and the relevance of some new, and old, vaccines. Vaccines evoke concerns different from other health interventions because many healthy people need to be vaccinated to achieve a protective public health benefit.

Several factors drive public questions and concerns: perceptions of business and financial motives of the vaccine industry and their perceived pressures on public institutions—such as during the H1N1 influenza response; coincidental rather than causal adverse events that are perceived as vaccine related; challenges in management and communication of uncertainty about risks[7] (including serious, albeit rare, ones); less risk tolerance for vaccines given to those who are healthy than for drugs given to treat an illness; scepticism of scientific truths, which later become untruths, or amended truths as new research becomes available;[8] elitism of a group of people that believe they should not risk vaccination of their child if enough other children are being vaccinated; and, in some cases, outright non-acceptance of scientific evidence such as in the case of antivaccine movements that persist in the belief that autism can be caused by thiomersal or the measles,

Key messages

- Public concerns about vaccines are not merely about vaccine safety, but are also about vaccine policies and recommendations, vaccine costs, and new research findings.
- Public decision making related to vaccine acceptance is complex and is neither driven by scientific nor economic evidence alone, but is also driven by a mix of scientific, psychological, sociocultural, and political reasons, all of which need to be better understood.
- The internet and new forms of social media have not only allowed for rapid and ubiquitous sharing of information—and misinformation—but have also allowed new methods of self-organisation and empowerment of newly founded online communities that argue against or for vaccines.
- Although communication of positive, evidence-based information about the safety of specific vaccines and their benefit–risk ratios to the public is crucial, communication alone will not stop public distrust and dissent against vaccines.
- Levels of public trust in vaccines are highly variable and context specific. To sustain or restore confidence in vaccines, a thorough understanding is needed of the population's—or subpopulation's—specific vaccine concerns, historical experiences, religious or political affiliation, and socioeconomic status.
- Core principles to be followed by all health providers, experts, health authorities, policy makers, and politicians include: engagement with and listening to stakeholders, being transparent about decision making, and being honest and open about uncertainty and risks.

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mumps, and rubella (MMR) vaccine, despite an abundance of scientific evidence that shows no causal effect.[9,10]

Although communication of candid, evidence-based information to the public about the safety of specific vaccines and their benefit–risk ratios is crucial, this information alone will not stop public distrust and dissent against vaccines. Public decision making related to vaccine acceptance is not driven by scientific or economic evidence alone, but is also driven by a mix of scientific, economic, psychological, sociocultural, and political factors, all of which need to be understood and taken into account by policy and other decision makers.

We discuss factors in the changing global environment that have precipitated what some in the specialty of climate change call "an erosion of trust",[11] caused by a small minority of climate change sceptics. The vaccine community faces similar challenges. We examine key determinants of trust, with specific examples in which public distrust undermined vaccine acceptance and interrupted immunisation programmes, and, then, what was done to restore trust. Finally, we outline ways to improve public trust including future research and actions that can be taken now.

***Panel 1*: Framework for analysing the development of public concerns about vaccines**

Prompters of public concern

Adverse events after immunisation—generally, such events that occur locally are stronger prompters of rumours, but an event reported in a distant location is also a possible prompt; publication of new research;[12] new recommendations or policy change (eg, removal of thiomersal from vaccines in the USA, stopping hepatitis B vaccination in schools in France); new products (ie, introduction of new product or change of current product source or product packaging); political motivations (ie, purposefully spreading rumours to undermine the government, other providers, or producers of the vaccine)

Factors that sustain public concern

Global spread of vaccine-related rumours; frequency of rumours (eg, occasional rumours *vs* persisting and strengthening rumours); media reports that amplify any prompter of public concern; historical bad experience that lowers public trust (eg, Pfizer's Trovan trial was perceived to cause childhood deaths in Nigeria, inadequate public information about the bovine spongiform encephalopathy outbreak in UK, dishonesty about HIV-infected blood supply in France);[13] socioeconomic marginalisation (ie, populations that have historically been marginalised with lower access to health services are less trusting of authorities); previous existence of self-organised community groups that can repurpose their experience to address vaccine concerns (eg, women's groups organised to question and stop human papillomavirus vaccine project in India[14])

Outcome and effects

Vaccine refusals (individual or group level); vaccine withdrawal (this can be a prompter of rumours and a consequence of rumours); vaccine-preventable disease outbreaks (eg, measles, pertussis, poliomyelitis)

The changing global environment

Background

Many proposed explanations exist as to why vaccines are questioned by the public, what exactly is being questioned, and what can be done to restore public confidence. One common perception is that waning public trust in vaccines is because vaccines have become a victim of their own success—whereby they have been so effective for prevention of disease that more attention has now been focused on the potential risks of vaccines than on the risks of the now less prevalent diseases they prevent. In high-income countries, lack of familiarity with vaccine-preventable diseases is present in the health-care community (eg, nurses, physicians, and others that administer vaccines),[6] many of whom are too young to have seen these illnesses.

Increased public questioning of vaccines in low-income countries, where vaccine preventable diseases are still prevalent, point to other underlying reasons for public distrust or dissent besides the absence of vaccine-preventable disease (panel 1). These reasons can be cultural, religious, or sometimes economic or political, as in the case of the polio vaccination boycott in northern Nigeria, where marginalised communities asserted their voice by refusing or challenging government-driven initiatives.[15]

Vaccine safety

Another perception is that vaccine safety is the primary concern of the vaccine-questioning public. Although vaccine safety is clearly important, and certainly the most monitored and addressed concern by national immunisation programmes and international organisations such as WHO and UNICEF, safety is not the only concern a growing number of individuals, communities, and even governments have about vaccines. Other concerns include affordability and relevance of new vaccines in different settings. Furthermore, the issue of vaccine safety is now being viewed in the framework of individual genetic predispositions to harm, raising fears that adverse events after immunisation are expressions of uncommon genetic susceptibilities.[16]

Diversity of vaccines

In the past decade, the global vaccine industry has mushroomed in terms of the number of companies involved and products in development. From 1995 to 2008, the number of vaccine companies that sought to create or manufacture vaccines doubled to 136, as did the number of prophylactic vaccine products in

development to 354.[17] The list of WHO prequalified vaccines now has 202 products from different manufacturers targeted against 20 infectious agents,[18] and the US Food and Drug Administration (FDA) list of vaccines available for immunisation in the USA consists of 72 products.[19] Most of these products are variations and combinations of vaccines that have existed for years, and thus are not really new, but the range certainly seems complex and confusing to both recipients and providers of vaccines.

Although the growing numbers of vaccines available or in development is impressive, the diversity of vaccines—including vaccines tailored to specific populations—has also contributed to public questioning of vaccine choices and the relevance of so many vaccines. Other concerns have arisen about the ability of low-income countries to afford the introduction of new vaccines, especially when access to even the least expensive vaccines is inadequate.[20]

Vaccine schedules

As new vaccines are introduced, vaccine schedules change. Schedules also vary across countries. These changes and differences in vaccine schedules further contribute to public questioning,[1,21] In the WHO listing of immunisation schedules by antigen and country,[22] for example, selection of a list of schedules for "tetanus and diphtheria toxoid childrens' dose" worldwide showed a listing of 72 countries with 29 different variations of diphtheria and tetanus schedules. Explanations for these programme differences include variations in the epidemiological aspects of the diseases and in the health-care financing and delivery systems between the countries. However, a substantial part of the variation cannot be justified on the basis of best public health practice, and some public questioning is understandable.

New research

Public concerns can also emerge after publication of new research, such as the 1994 publication by Talwar and colleagues[12] about an antipregnancy vaccine, in which the mention of tetanus toxoid used as a carrier protein was misinterpreted. A pro-life Catholic group, Human Life International, consequently suggested that tetanus vaccines could cause sterilisation, resulting in vaccine scares in Mexico, the Philippines, Tanzania, and Nicaragua. Concerns were also raised by the 1998 publication by Andrew Wakefield that proposed links between the MMR vaccine, autism, and bowel disease. Although the research was later retracted, Wakefield's misuse of that work—including statements in the press conference that were not included in the published report[23]—catalysed widespread fears, some of which persist today.

Government policies

Policy choices or recommendations are also a key public concern. Such choices that have prompted public debate and affected public trust include: legislation requiring vaccination for school entry; the US Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) recommendation in July, 1999, that thiomersal be removed from childhood vaccines; and the decision in France in 1998 to withdraw the hepatitis-B-vaccination programme from schools.[24]

Public trust is challenged particularly when public authorities disagree, such as was the case in 1998 when the French Government suspended the use of the hepatitis B vaccine, which went against the recommendation of WHO and the viral hepatitis prevention board (an expert committee convened by WHO).[25] The result of this decision was that 10 years after the temporary vaccine suspension, three-dose vaccine coverage with hepatitis B vaccine was still only 30%.[26]

Another example of such disagreement was the Japanese Government's decision to suspend the pneumococcal conjugate vaccine Prevnar (Pfizer, New York, NY, USA) and the *Haemophilus influenzae* type b vaccine ActHIB (Sanofi-Aventis, Bridgewater, NJ, USA), while investigating suspected links of these vaccines with the death of four children, which prompted widespread media coverage. A Google search for "Japan" and "Prevnar" and "2011" on April 7, 2011, 1 month after the vaccines were suspended, showed more than 85 000 reports globally. Of the first 100 results listed, only three were about the decision to resume use of the vaccines on March 30, 2011; these three reports were 45th, 91st, and 93rd in the list. When the same search was done on WHO and CDC websites, no information was available on either the suspension or resumption of the two vaccines.

New media and horizontal communication

Democratisation movements and the advent of the internet have changed the environment around vaccines from top-down, expert-to-consumer (vertical) communication towards non-hierarchical, dialogue-based (horizontal) communication, through which the public increasingly questions recommendations of experts and public institutions on the basis of their own, often web-based, research. Such public questioning is not unique to vaccines, but part of a broader environment of increasing public questioning and the emergence of dissent groups, particularly in areas that include risks such as climate change.

The internet, social media—which allows interactive exchange between many users—and mobile phone networks have shifted the methods and speed of communication substantially, allowing information about vaccines and immunisation to be gathered, analysed, and used—especially through blogs—very differently compared with even a decade ago. The amount of information available has increased greatly, including scientifically valid data and evidence-based recommendations alongside poor quality data, personal opinions, and misinformation.

Media attempts to balance coverage by provision of equal opportunity to all viewpoints exacerbates the challenges to public confidence in vaccines by allowing outlier views and small extremist opinions the same media space as views validated through a rigorous process of peer review by the scientific community. This disproportionate share of outlier views has been further amplified by celebrities—such as Jim Carrey or Jenny McCarthy—who encourage parents to question vaccines, often telling highly emotional stories of children who were perceived to have been harmed by vaccines.[27]

The emergence of social media tools, such as Facebook with more than 500 million users globally,[28] has helped create new methods of self-organisation and empowerment of newly founded virtual communities both locally and across wide geographical areas, building constituencies that argue against or for vaccines.[29–31] Although some of these networks have a national focus, they are also quick to pick up and amplify events occurring in other countries that support their cause.

The new mix of highly varied and often conflicting information contributes to the scepticism of some vaccine consumers. These views need to be far better understood as they are developing, rather than when vaccination rates start to decline because of distrust.

Determinants of public trust in vaccines

Public trust in vaccines is a complex issue that often has many converging determinants. Research into environmental-risk communication has identified three factors that affect the extent to which an individual or institution is trusted: perceptions of knowledge and expertise, openness and honesty, and concern and care.[32] The credibility of vaccine information, for example, is influenced by the perceived trustworthiness of the messenger—whether a government authority, the vaccine industry, a health provider, a friend or colleague, or the media. To address persisting concerns about oral polio vaccines causing sterilisation, especially in poorer, marginalised Muslim populations in northern Nigeria and Uttar Pradesh, India, WHO and the Global Polio Eradication Initiative partners convened meetings with the Organisation of Islamic States, as trusted intermediaries or brokers with the public, to successfully rebuild trust in the polio vaccine in their Muslim constituencies. Similarly, when fears spread through Catholic pro-life groups that the tetanus vaccine had sterilising elements, WHO officials requested that the Vatican choose the laboratory in which the vaccine was tested, because it was a trusted institution for these groups (Ciro de Quadros; Albert B. Sabin Vaccine Institute, Washington, DC; personal communication).

Whether the public perceives new information about vaccines as honest and not hiding information about risks also affects public trust in vaccines. Similarly, openness and transparency in decision making about new vaccine policies or research processes can influence the trust of the public or interest groups in the population. The suspension of the human papillomavirus vaccine demonstration project in India, in April, 2010, is an example of the potential effect of distrust, because of inadequate open dialogue with groups who question the vaccine.[14]

Individual and group experiences also affect public willingness to trust vaccines.[13] Public trust of the internationally driven polio vaccination campaign in northern Nigeria, for example, was undermined by Pfizer's trial of the Trovan vaccine in northern Nigeria, because child deaths were suspected to be linked to the trials.

The personal nature of a particular vaccine concern is another determinant of trust, and can mean that individuals or groups are overly trusting because of an eagerness for an answer to their concern. In their search for answers to questions such as "why does my child have autism?", individuals and groups might be willing to trust information that is not scientifically proven if it addresses their concerns.

To improve understanding and address determinants of public trust in vaccines, and the potential effect of these determinants, research is needed not only into individual determinants of trust, but on understanding what mix of factors is most likely to sustain, or damage, public trust. Risk events, such as an adverse events after immunisation, or even perceptions of risk, such as fears of vaccines causing sterilisation or autism, can be amplified or attenuated, depending on how the event or perception of the event is communicated to, and interpreted by, individuals, institutions, or the media.[33]

Case studies

The following case studies describe examples of how vaccine risk concerns were prompted and sustained by individuals—from religious leaders to scientists and health experts, governmental and non-governmental institutions, religious and other interest groups, and the media. The tipping point, whereby vaccines were refused or programmes were disrupted because of fears, was due to a convergence of events, creating a "social amplification of risk".[33]

Thiomersal and autism

Thiomersal, a compound containing ethylmercury, has been used to prevent bacterial contamination in biologics since the 1930s. In 1997, the FDA noted that, in view of the increasing number of vaccines given in early infancy, the total amount of ethylmercury (as thiomersal) might exceed the level set for methylmercury by US Environmental Protection Agency guidelines. In a period of increasing concern about poisoning from mercury in the environment, the AAP and CDC issued a joint statement in 1999 asking vaccine makers to remove thiomersal from childhood vaccines as soon as practical.[34] This statement, issued to show caution and assure the safety of vaccines, paradoxically supported

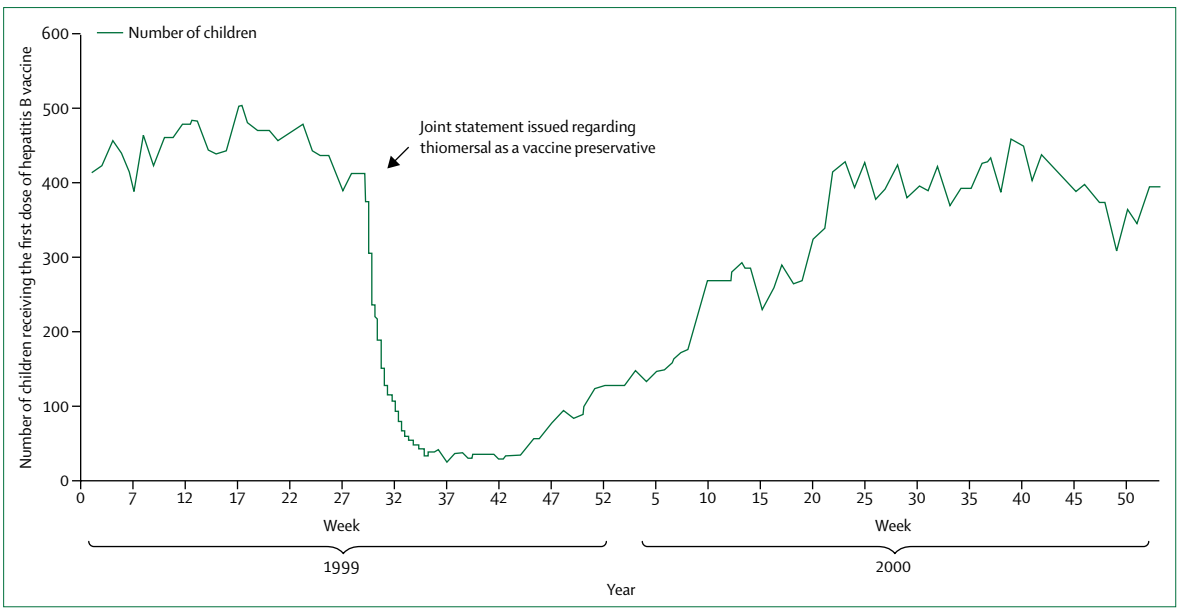

***Figure 1*: Number of children who received the first dose of hepatitis B vaccine less than 5 days after birth (USA, 1999–2000)**
Data from the US Centres of Disease Control and Prevention's morbidity and mortality weekly report.[38]

the argument of those suggesting that vaccines were contributing to what was called an epidemic of autism. Public concern was fuelled by organised groups of parents convinced that their children's autism was caused by mercury-containing vaccines, who prepared to seek compensation through the US National Vaccine Injury Compensation Program; a series of hearings by the chair of an oversight committee in the US House of Representatives who believed his own grandchildren had been harmed by vaccines; and studies and testimonials in public forums, by scientists and celebrities who are now discredited.

Since 1999, many studies have failed to support any causal relationship between thiomersal and autism.[35,36] The absence of this compound from childhood vaccines in the USA for almost a decade has not altered the frequency of autism. After exhaustive review, no evidence has been identified by the vaccine court, a component of the US Vaccine Injury Compensation Program, or the US Institute of Medicine to justify compensation of claimants on the basis of thiomersal in vaccines.[10]

This case is an example of the perverse consequences of application of the precautionary principle, which is applied when there is scientific uncertainty and when an intervention is deemed necessary before harm occurs.[37] The AAP and CDC joint statement showed the transparency of vaccine policy, but it did not necessarily earn trust from those convinced that vaccines are harmful, and in fact prompted more questioning of the safety of vaccines. Removal of thiomersal from childhood vaccines in the USA also created tension between the USA and global vaccine programmes, especially in developing countries where direct vaccine and logistical costs would be prohibitive if thiomersal were removed and single-dose vaccines were instead mandated. Additionally, removal of this compound caused an unexpected temporary decline in rates of hepatitis B vaccination in infants in the USA (figure 1). However, the precautionary measure was based on scientific evidence available at a given point in time and a value system based on the best interests of the public. Had a causal link between thiomersal and autism been discovered, the recommended early removal of thiomersal would have been lauded by the public.

Haemophilus influenzae type b vaccine in India

Similar tensions between experts occurred in India in relation to introduction of the *H influenzae* type b pentavalent vaccine combined with diphtheria, poliovirus, and tetanus, and hepatitis B virus. Introduction of this vaccine was challenged by Puliyel and colleagues,[39,40] who asserted that the disease burden in India did not justify addition of the expensive vaccine.

Puliyel and colleagues also claimed that the disease burden data were misrepresented by the GAVI Alliance and WHO.[41,42] Indian pediatricians contested their assertions with evidence on the disease burden of *H influenzae* type b in India, which they felt made a compelling case for introduction of the vaccine against this disease.[43] Others accused Puliyel of leading an antivaccination lobby.[44]

Puliyel and academic and government colleagues who share his view reject the antivaccination label. In a statement published in 2010, they wrote that "we are a group of pediatricians, healthcare activists, teachers in public health, and bureaucrats who have championed

universal immunisation in India throughout our working lives". They went on to note that they were "taken aback" by the fact that their questioning of the appropriateness of introducing the *H influenzae* type b vaccine in India was misconstrued as a broad anti-vaccination movement.[31]

Although introduction of the vaccine was endorsed by WHO and the Indian National Immunization Technical Advisory Group (INITAG), opposition from Puliyel and colleagues led the Indian Health Ministry to stall introduction of the vaccine. The Health Ministry convened an independent expert group to re-examine WHO and INITAG's recommendations. This group has since concluded that the government should move forward and accept the GAVI Alliance's financial support to the Government of India to allow it to proceed with the introduction of the vaccine. Nonetheless, the Indian press picked up the debate and widely publicised Puliyel's concerns, which will probably not be forgotten.

MMR vaccine and autism

The public's eagerness for answers to their felt needs is another determinant of trust. Wakefield's claims in 1998 that the MMR vaccine could cause autism was embraced by parents who were eager to find a reason for their child's autism. His suggestion that a single-antigen measles vaccine should be considered as a safer alternative to the MMR vaccine also gave the parents a solution. When the then Prime Minister Tony Blair refused to reveal whether his young son had been given the MMR vaccine, Wakefield's findings seemed validated. Although many subsequent studies failed to reproduce Wakefield's findings,[9] and his research paper was formally retracted,[45] the distrust generated around the MMR vaccine contributed to declines in MMR vaccine coverage and consequent measles outbreaks.[46] Research done in the UK by the Department of Health showed that overall trust in the MMR vaccine has recovered at least in Britain, where the controversy began.[47] Wakefield continues public speaking engagements internationally to perpetuate his views by appealing to vaccine-sceptical parents—even after being scientifically discredited. The groups that still champion Wakefield's views, especially in the USA, are a stark example of the vulnerability of public confidence in vaccines.[27,48,49]

Tetanus vaccine and sterilisation

In the case of fears related to sterilisation caused by tetanus vaccines in the early 1990s, a Catholic organisation with membership in more than 60 countries, popular media, religious and political leaders, and legislative authorities converged to amplify perceived risks of sterilisation associated with vaccination, which led to reduced uptake of the tetanus vaccine and vaccine programme disruptions.

In 1994, a research article on a birth control vaccine[12] made reference to the use of tetanus toxoid as a carrier protein. Although the birth control vaccine had no relation with tetanus immunisation, it created a perceived connection between tetanus vaccination and contraception that travelled widely thoughout the internet; Human Life International communicated this perceived connection to their members in more than 60 countries. In the Philippines, the tetanus vaccination campaign was interrupted by a court injunction. The subsequent panic led to a 45% drop in tetanus vaccination coverage between 1994 and 1995.[50] In Nicaragua, Catholic Cardinal Obando, a member of Pro-vida, played a substantial part in stopping the tetanus immunisation campaign in that region.[47] In Mexico, the Comite Pro-vida accused the government of genocide, claiming that the tetanus vaccine caused abortion. Although the damage caused by these antivaccination campaigns has been largely mitigated by proactive measures by the Pan American Health Organization—through engagement with the media and the Vatican—the notion that vaccines contain sterilising substances periodically resurfaces, most recently in the polio campaigns in Nigeria and India.[51]

Oral polio vaccine and sterilisation

In northern Nigeria, religious and political leaders, led by the chairman of the Supreme Council for Sharia in Nigeria, Datti Ahmed, boycotted the polio vaccine in 2003, claiming that the oral polio vaccine was contaminated with HIV and could also cause sterilisation in those vaccinated, fuelling widespread public distrust. Political and cultural disparities between northern and southern Nigeria also influenced the willingness of the people in the north to sign-up to a mandate thought to be imposed by the head of state, and international health bodies.[15] Memories of the Trovan trial in 1996, during which children died, were still vivid in the minds of many, undermining their trust. Although subsequent investigation did not attribute the children's deaths to the drug being tested, the trial was deemed illegal because of unethical conduct.[52] The legal proceedings of the trial, which were undertaken in the northern state of Kano, took place in the background of the polio vaccination boycott.

The boycott of oral polio vaccination in Kano State lasted 11 months and poliomyelitis cases in Nigeria rose from a nadir of 56 in 2001 to 1143 in 2006. Spread of the poliovirus in Nigeria led to outbreaks in 15 other sub-Saharan nations,[53] and spread as far as Indonesia where 303 cases were all traced to Nigeria.[54]

This boycott was a wake-up call to the Global Polio Eradication Initiative on the need for better engagement with both local leaders and affected communities. At the 60th World Health Assembly, a report on poliomyelitis[55] called on member states to improve engagement with local and national leaders and with affected communities. Although calls for public engagement are not new, the polio experience has prompted detailed, research-driven communication and public engagement strategies.

The Global Polio Eradication Initiative has done extensive, block-by-block research in some settings to understand who are locally trusted sources of vaccine information and who are the trusted providers of vaccines, and to understand the reasons behind vaccine refusals.[56] In Pakistan, research showed that some of the public resistance was actually among health workers, who felt underpaid and perceived the initiative as being imposed from outside Pakistan, and was not locally owned.[57] Understanding how to build and restore trust can only be addressed with research.[58] In the case of the Global Polio Eradication Initiative, the need for improved understanding of specific public concerns and reasons for distrust came only in the face of a crisis of confidence. The lesson learned was that not only is research within the local communities needed, but that it is needed early on in the planning of vaccination programmes, well before a crisis occurs.

Effects of public distrust

Evidence about the effects of misinformation, rumours, and antivaccine groups on vaccine coverage and consequent disease outbreaks in many countries is well documented. In addition to the polio, tetanus, and MMR vaccine examples, increases in pertussis outbreaks have occurred in Russia,[59] Japan, the USA, Sweden, and England and Wales after antivaccine activity.[60] In France, the political decision to suspend hepatitis B vaccines in schools exacerbated public concerns associating hepatitis B vaccines with autism, multiple sclerosis, and leukaemia and led to low levels of hepatitis B vaccination.[61] In the Ukraine, scares and negative public reaction to a measles and rubella vaccination campaign led to quarantining of the vaccine and suspension of the campaign, which was targeting 7·5 million people, but only reached 116 000.[62]

In all of these situations, management of the effects of declines in vaccine uptake, consequent disease outbreaks, and loss of public trust in the vaccines has taken a toll on human and financial resources in addition to long-term reputational costs to individual vaccines and immunisation programmes.

New methods of communication, dialogue, and engagement are urgently needed across all vaccine stakeholders—vaccine experts, scientists, industry, national and international health organisations, policy makers, politicians, health professionals, the media, and the public. No single player can reverse the vaccine confidence gap.

The way forward: who needs to do what?

The foregoing examples show that the process of building, rebuilding, and sustaining public trust in vaccines is highly variable and depends on a thorough understanding of the community and its socioeconomic status, previous experience, views of those they trust (and distrust) including religious or political leaders, and understanding of the risks and benefits of vaccines versus the diseases they prevent.

Traditional principles and practices of vaccine communication remain valid,[63] especially those that ensure timely and accurate communication of information about where, when, and why vaccines are given, and those that ensure mutual respect in health provider–patient interaction. However, additional emphasis should be placed on listening to the concerns and understanding the perceptions of the public to inform risk communication, and to incorporate public perspectives in planning vaccine policies and programmes.

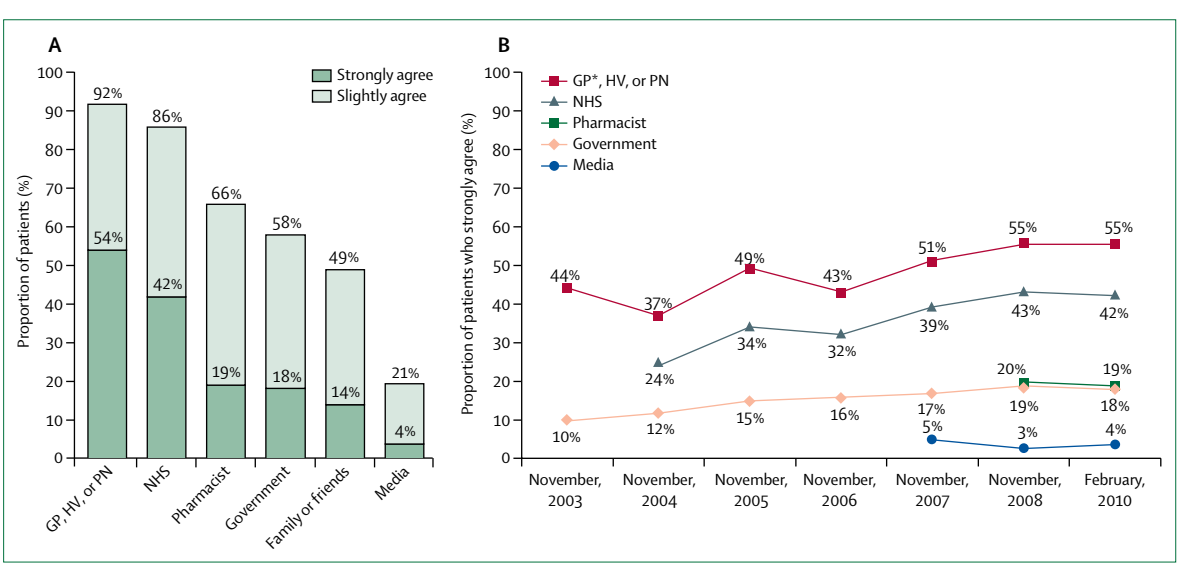

***Figure 2*: Research into who parents trust**

Data were provided by David Salisbury (Department of Immunisation, Department of Health, UK). (A) Who parents trust to give advice about immunisation (2010); data are for parents of children aged 0–4 years (n=1730). (B) Who parents trust to give advice about immunisation (2007–10); data are for parents of children aged 0–2 years (n=1142). GP=general practitioner. HV=health visitor. PN=practice nurse. NHS=national health service. *GP data gathered before 2007.

***Panel 2:* Actions needed**

- In view of the heterogeneity of populations, and the local specificity of vaccine concerns and trust relations, strategies to build public trust need to be locally tailored and not prescriptive in recommendations of what specifically needs to be done by various stakeholders to build confidence in vaccines.
- Evidence-based approaches used in risk communication[76] should be adopted as core principles by all health providers, experts, health authorities, policy makers, and politicians when communicating information about vaccines. These approaches include engagement with and listening to stakeholders, and being transparent about decision making, and honest and open about uncertainty and risks.
- A systematic approach is needed to listen to public concerns. As with infectious diseases, where surveillance is essential for disease control, systematic monitoring of dynamic and evolving vaccine rumours, concerns, and refusals is crucial to guide prompt responses to build and sustain public confidence. Such a surveillance system is being trialled at the London School of Hygiene and Tropical Medicine.[77]
- Decision and policy makers cannot assume what the public wants without undertaking social science and decision science research. The vaccine community demands rigorous evidence for vaccine efficacy and safety and the technical and operational feasibility of initiating a new vaccine initiative or introducing a new vaccine, but have been negligent in demanding evidence on the social and political feasibility of introducing new vaccines and the factors that determine the local acceptability of vaccines.
- Models of multidisciplinary research for vaccine introduction are emerging[78,79] and need to be expanded. These models include not only technical and operational assessments, but also research into social and political factors that need to be considered in planning the introduction of vaccines. The Global Polio Eradication Initiative has shown that monitoring of public concerns needs to be continuous and responsive, and hand in hand with the monitoring of technical strategies.[54]

To build public confidence, it is key to understand what drives public trust in each community,[64–66] and what are the local perceptions of vaccines and their risks.[1,67–72] According to a US National Research Council report, risk communication "emphasizes the process of exchanging information and opinion with the public".[73] Building public trust is not about telling them what they need to understand better, and it is not merely about being clearer or teaching parents about risk–benefit decision making. Trust is built through dialogue and exchange of information and opinion. Valuable models can be drawn from environmental-risk research, which emphasise the importance of listening to public concerns and can protect against simplistic solutions to complex problems.[74]

Research is needed to understand who the public trusts. The UK Department of Health, for example, continues to monitor not only public perceptions of different vaccines, but also who the public trusts (figure 2). Similar studies are in progress in academic institutions[75] and in the CDC.[1] Such efforts should be encouraged and funded.

The immunisation enterprise is a complex matrix involving academia, government, industry, private clinicians and other health providers, and public-health systems. Every one of these entities is vulnerable to public mistrust. Improved communication, dialogue, and trust-building across these entities is essential. The private sector is very conscious of consumer confidence levels as a metric of success and acceptance of their products. The public health community needs similar attentiveness to ensure consumer confidence if we are to achieve the potential benefits of new and existing vaccines (panel 2).

Conclusion

Vaccination is a complex social act that effects both direct, perceived self-interest, the interest of one's children, and the broader community. The decision leading to immunisation remains a personal summation of each individual's perception of the complexity of information they receive and their trust in the institutions that produce, legislate, and deliver vaccines. For vaccines to realise their full potential in protection of health, public and private health practices need to take into account the range of social and political factors that affect the public's willingness to accept vaccines.

The immunisation community, including scientists, policy makers, and health providers, needs to come to terms with the reality that individuals and groups will continue to question and refuse vaccines. Extremist antivaccination groups whose minds will not change will exist. Many people—the majority—who accept vaccines could change their mind. The focus should be on building and sustaining trust with those who accept and support vaccines, while working to understand and address the growing confidence gap.

Contributors

HJL, LZC, SLK, and JE outlined the report. HJL prepared the first and subsequent drafts with input from LZC, SLK, JE, SR. All authors read and approved the final draft.

Conflicts of interest

JE received funding from Novartis for a pneumococcal advisory meeting and as a data and safety monitoring board member for meningococcal and typhoid vaccines. SR edits the *Journal of Health Communication*, with faculty appointments at Tufts School of Medicine and George Washington School of Public Health and Health Services. SR contributed independently of his principal employer, Johnson & Johnson. Some technical work, travel (LZC and SLK), and meetings relevant to this work were funded by the Bill & Melinda Gates Foundation. The funding organisation had no role in the drafting or direction of this report. HJL declares that she has no conflicts of interest.

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