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.

Introduction

On May 8, 1980, the World Health Assembly certified the world free of naturally occurring smallpox. Since then, an unprecedented rise in new vaccine development has occurred (table 1). 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.

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.

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. 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). In the past, some accidents were a result of suboptimum manufacturing, as was the case in the so-called Cutter incident; 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, poliomyelitis, and tetanus as public health problems
vaccine with recombinant DNA technology, the technologies began with the development of a hepatitis B virus conjugate vaccine in 1987, and conjugate vaccines, which resulted in the development of the seven-valent pneumococcal conjugate vaccine in 1990. 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. 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. 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 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, the application of glycoconjugation for polysaccharide vaccines, which resulted in the development of the conjugate H influenzae type b vaccine in 1987, 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. 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. 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

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<table>
<thead>
<tr>
<th>Cell culture</th>
<th>Recombinant DNA, virus-like particles</th>
<th>Conjugation</th>
<th>Combinations</th>
<th>New adjuvants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s</td>
<td>Rabies</td>
<td>Hepatitis B</td>
<td>Hib</td>
<td>-</td>
</tr>
<tr>
<td>1990s</td>
<td>Japanese encephalitis, varicella, hepatitis A, rotavirus</td>
<td>Acellular pertussis Lyme</td>
<td>Men C</td>
<td>DTP-Hib</td>
</tr>
<tr>
<td>2000s</td>
<td>Live influenza, rotavirus, herpes zoster, H1N1 influenza</td>
<td>HPV</td>
<td>PnC-7, PnC-10, PnC-15, Men ACWY</td>
<td>Hepatitis B and hepatitis A; DTA-Pf and hepatitis B; Men ACWY; MMRV</td>
</tr>
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Table 1: New and improved technologies and resulting vaccines (from 1980s to 2000s)

<table>
<thead>
<tr>
<th>Description</th>
<th>Advantages</th>
<th>Drawbacks</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killed microorganisms</td>
<td>The causative agent is inactivated by chemical or physical treatments</td>
<td>Efficacious</td>
<td>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</td>
</tr>
<tr>
<td>Live attenuated microorganism</td>
<td>The causative agent is live, but it has lost the ability to cause the disease</td>
<td>Efficacious; can induce a protective immune response</td>
<td>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</td>
</tr>
<tr>
<td>Subunit</td>
<td>Vaccines contain purified portions of the causative agents</td>
<td>Toxins are inactivated chemically if not properly inactivated they can cause disease (eg, several accidents in the 1950s with diphtheria not fully inactivated); such inactivated vaccines cannot provoke the disease; if recombinant forms of the selected components are used, the pathogen need not be cultivated</td>
<td>Identification of the few protective components from the pool of molecules in the pathogen is usually complex and time consuming</td>
</tr>
<tr>
<td>Subunit conjugated</td>
<td>A polysaccharide component of the causative agent is chemically linked to a protein carrier</td>
<td>The conjugated polysaccharide, which is poorly immunogenic on its own, becomes immunogenic</td>
<td>Need to grow the pathogen in vitro to obtain the capsular polysaccharide; capsule not always immunogenic; too many capsule types</td>
</tr>
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Table 2: Different approaches to vaccine design in the pregenomic period through application of Louis Pasteur’s principles
but substantially reduced disease caused by these serotypes in unvaccinated adults. Similar herd effects have been reported for meningococcal C conjugate vaccine. 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.

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. 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.

### 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 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.

### 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. 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). 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 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. Structural studies have led to improved understanding of the various mechanisms by which different paramyxoviruses use their attachment glycoproteins to...
hijack specific protein and glycan cell-surface receptors for viral entry. 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, 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. This approach has been used to develop some expanded range of targets for preventive and therapeutic vaccines. Ideally, such markers would allow early identification of unsafe vaccine candidates and guide selection of the most effective vaccine combinations.

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. By contrast, bacterial genomics has provided a long list of new antigens. Reifinement 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.

DNA and RNA vaccines

Although DNA vaccines were initially thought to be a promising technology, studies have yielded disappointing results, 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. Research into this approach for HIV and cancer vaccines continues. 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.

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. Additionally,
assessments 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.\textsuperscript{21}

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.\textsuperscript{21} 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.\textsuperscript{3} 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.\textsuperscript{21} 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,\textsuperscript{21} 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.\textsuperscript{22} However, protein homologies are many and are usually not associated with a risk of autoimmunity.\textsuperscript{22}

Such mimicry studies are of relevance to polysaccharide antigens that are known to mimic human cell-surface structures such as neural adhesin molecule.\textsuperscript{27}

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\textsuperscript{21,23} and through analysis of cellular phenotypes at the site of vaccine injection and in draining lymph nodes.\textsuperscript{23} 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,\textsuperscript{34} 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.\textsuperscript{21}

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.\textsuperscript{3} 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.\textsuperscript{24} 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. 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-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. 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. 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.

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. 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. Additionally, detailed knowledge of oil-in-water adjuvanted vaccines was gained from widespread use, confirming the safety that had been shown in previous studies. 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.

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. 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. 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; 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. For this reason, introduction of the pneumococcal conjugate vaccine in South Africa has
Challenges for the next decade

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 shigellosis.
- 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. However, vaccines that are in development or might be developed will target...
diseases specific to poorer countries, such as tuberculosis, typhoid fever, shigellosis, 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. 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. 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. However, as in the past, success will depend on our ability to successfully implement vaccination programmes that fulfill 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. PHI has received honoraria from Novartis, GlaxoSmithKline, and Sanofi Pasteur, and is a consultant for Glycovaixin, Wittycell, and DBV Technologies.

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