**Review**

**Twenty-first century vaccines**

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In the twentieth century, vaccination has been possibly the greatest revolution in health. Together with hygiene and antibiotics, vaccination led to the elimination of many childhood infectious diseases and contributed to the increase in disability-free life expectancy that in Western societies rose from 50 to 78–85 years (Crimmins, E. M. & Finch, C. E. 2006 Proc. Natl Acad. Sci. USA 103, 498–503; Kirkwood, T. B. 2008 Nat. Med 10, 1177–1185). In the twenty-first century, vaccination will be expected to eliminate the remaining childhood infectious diseases, such as meningococcal meningitis, respiratory syncytial virus, group A streptococcus, and will address the health challenges of this century such as those associated with ageing, antibiotic resistance, emerging infectious diseases and poverty. However, for this to happen, we need to increase the public trust in vaccination so that vaccines can be perceived as the best insurance against most diseases across all ages.

**Keywords:** vaccines; vaccination; infectious diseases

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1. **THE NEED TO INCREASE PUBLIC CONFIDENCE IN VACCINATION**

Until very recently, vaccines had been developed following the Pasteur example of inactivating and injecting the micro-organisms causing the diseases [1]. These primitive technologies, mostly developed during the first half of the twentieth century, led to crude vaccine preparations that have nevertheless been very successful in the conquest of diseases. However, they were often associated with some safety concerns. For instance, although it was instrumental in the eradication of the disease, the smallpox vaccine was essentially developed with a technology of 1796, and was associated with cases of generalized vaccinia, encephalitis and myocarditis. The first rabies vaccine, grown in mouse brain cells, was associated with the occasional induction of encephalitis owing to vaccine-related autoimmune responses against the brain protein myelin [2]. Even the Sabin oral poliomelitis vaccine, developed during the 1950s, was associated in one case per million with paralytic disease in vaccinees and contacts. Some of the other first generation vaccines were also known to exert a significant reactogenicity. Therefore, it was quite understandable that some public fears were associated with vaccination during the first part of the twentieth century.

Although, none of these vaccines is used any longer, at least in Western countries (table 1), there is still a deficit of public trust which is hampering the optimal control of some vaccine-preventable diseases. This is owing to the perception that vaccines are great tools to fight fatal diseases but may occasionally be dangerous. This is enhanced when the risk of infection is decreasing as a result of generalized vaccination against a particular target disease and it is a paradox characteristic of a wealthy society. There is a false perception that some diseases are not or are no longer dangerous. For example, many people consider measles to be an entirely benign infection and forget the high toll of morbidity and mortality it can cause: measles epidemics do occur today in European countries because the rejection of vaccination has resulted in insufficient vaccination coverage. Similarly, there was a major epidemic of diphtheria in Russia owing to disruption of the health system in the former USSR and a reduced level of vaccination. This prejudice against vaccines has fostered the perception that vaccines are great but dangerous, and throughout the entire twentieth century, people regularly attributed to vaccination all those diseases of unknown cause. For instance, in the absence of a known cause of the rise of autism, many people concluded that it had to be caused by vaccination. First, they associated autism with measles, mumps and rubella vaccination; then, when that was disproved scientifically, others associated autism with the use of thimerosal, a mercury compound used until recently to maintain the sterility of vaccines [3]. Now, even after the association of thimerosal with autism has been scientifically disproved, there are still some fundamentalists who refuse to accept the scientific evidence and insist that autism is caused by vaccination. Another example is war veterans. When they come back from the drama of the war with various health problems, such as in the case of the Gulf War [4], people like to attribute their disabilities to vaccines rather than to the brutality of the war. Similar clinical pictures were observed in the soldiers fighting in the American Civil War, at a time when vaccines (except for one) did not exist. Another phenomenon that has happened during the past century is the increase of allergies in developed countries: being of unknown cause, many have associated it with vaccination.
Table 1. Vaccines associated with safety concerns that are no longer used.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>smallpox</td>
<td>generalized vaccinia, encephalitis, myocarditis</td>
</tr>
<tr>
<td>Sabin oral polio</td>
<td>paralytic disease in vaccinees and contacts</td>
</tr>
<tr>
<td>measles high dose</td>
<td>increased mortality from all causes in females</td>
</tr>
<tr>
<td>diphtheria, pertussis,</td>
<td>febrile seizures and</td>
</tr>
<tr>
<td>tetanus (whole cell P)</td>
<td>encephalopathy (disproved)</td>
</tr>
<tr>
<td>rotavirus (Rotashield)</td>
<td>intussusception (bowel obstruction)</td>
</tr>
<tr>
<td>bacillus Calmette–Guérin (BCG) (tuberculosis)</td>
<td>disseminated BCG infection</td>
</tr>
<tr>
<td>thimerosal</td>
<td>autism, neurodevelopmental delays (disproved)</td>
</tr>
</tbody>
</table>

Box 1. New tools will continue to improve vaccine safety.

- Screening for sequences homologous to proteins encoded by the human genome to remove sequences mimicking self antigens
- Immunohistochemistry to check cross reactions with human tissues
- Multiple cytokine induction to profile the Th1/Th2 immune responses
- Profile of cytokines induced by novel adjuvants and vaccines to predict the induction of expected immune response and the potential for autoimmunity
- Availability of well-controlled cell lines to avoid the use of undefined non-controlled cell substrates for vaccine production such as brain extracts (rabies), whole animals (smallpox), primary monkey kidney cells (polio Sabin). These may induce autoimmunity or contain undefined viral/prion contaminants
- Control of cell lines for prion proteins
- Simulation of immune response data from different immunization regimens
- Mathematical models of disease, biomarkers, immune response kinetics, efficacy and safety
- Mouse–human cross-over studies for understanding role of Toll-like receptors (TLRs)
- Animal and in vitro models to test disease enhancement (RSV, influenza and measles)
- Large phase III and phase IV studies to exclude statistically rare events

2. NEW TOOLS TO INCREASE PUBLIC CONFIDENCE

The perception that vaccination may be dangerous has been a major concern for vaccine developers and regulatory agencies that during the past few decades have been working hard to improve vaccine safety. First, all those vaccines associated with major safety concerns, such as smallpox, oral polio, whole cell pertussis and high dose measles, have been discontinued or are going to be discontinued soon (table 1). Second, the new technologies minimize the risks associated with the new generation of vaccines. Highly purified components of known molecular entity, recombinant antigens, polysaccharides conjugated to purified proteins and new antigens discovered by genomics have allowed the development of a new generation of molecularly tailored vaccines that are well characterized and intrinsically safer than the crude preparations of the twentieth century. Live-attenuated vaccines that in the past were derived by random passages and mutagenesis today have been replaced by strains with molecularly designed attenuating mutations or by vectors designed to immunize but not replicate. Finally, in the era of the technological revolution, we have plenty of new tools to predict safety risks of new vaccines. For instance, screening the vaccine candidates for sequence homology with the human genome allows identification and removal of those antigens that may have a risk of inducing autoimmunity that has so often been a problem in the past. New tools that will continue to increase vaccine safety are listed in box 1.

However, elimination of the vaccines with safety concerns and minimization of the safety risks in present and future vaccines is still not going to be enough to gain public trust in vaccines. We need to educate people that, even in developed countries, infectious diseases are still around us and are a real threat if we do not remain on the alert and if a preventative approach is not undertaken. Therefore, people need to think about vaccines when they are healthy, because vaccination is the best insurance against diseases that will be present in the twenty-first century. We need to remove from the minds of people the perception that vaccines are dangerous and to be avoided, since this is no longer true. Health policy-makers should also actively promote this message, starting from the consideration that vaccination has contributed more than any other medical intervention to the reduction of human diseases.

3. TWENTY-FIRST CENTURY VACCINES

Vaccines were developed in the twentieth century to address the needs of a society where morbidity and mortality caused by infectious diseases in the early years of life was the major health challenge. Thanks to the success of vaccines, in the twenty-first century people live longer, and we should consider how vaccination can be redesigned to meet the needs of healthcare systems that are struggling to cope with the new longevity.

Today vaccines address mostly infant diseases and we have more than 10 vaccines recommended in Western countries for infant vaccination, one (papillomavirus) recommended for adolescent women and one (influenza) recommended for the elderly. In developing countries, there are only five recommended vaccines, all for infants. However, thanks to the technological revolution, genomics and the great progress in immunology, today it is possible to design vaccines able to prevent many of the diseases of modern society. For instance, we could develop a vaccination plan where pregnant women receive a booster vaccine during the third trimester to generate and passively transfer to the foetus antibodies against those diseases of the first few days or months of life, such as group B streptococcus (GBS), tetanus, hepatitis B, meningococcus, pneumococcus, respiratory syncytial virus (RSV),...
influenza, using the strategy that has evolved naturally to protect newborns. Infants would then be vaccinated starting at four to five months of age to build their own active immunity. The next vaccination event would be in adolescents, who would receive those vaccines that prevent the chronic diseases and cancer associated with infectious diseases, such as papillomavirus (associated with ovarian cancer), hepatitis C (which is associated with liver cancer) and chlamydia (associated with infertility) and those vaccines that would be useful during pregnancy, such as cytomegalovirus (CMV) and GBS. Some vaccines like CMV and Epstein–Barr virus (EBV) also have the potential to slow ageing of the immune system, one of the major problems beyond the age of 50.

When the immune system starts to wane, vaccination could be used to fight, delay or eliminate those diseases that are typical of a modern ageing society. These are resurgent infectious diseases, such as influenza, pneumococcus, RSV, those diseases associated with the risk of hospitalization (mostly nosocomial diseases) and cancer.

Finally, there are numerous other health risks in modern society that could be minimized by using vaccination as an insurance. These include (i) prevention of those infections caused by antibiotic resistant microorganisms that are a major threat during hospitalization, such as Staphylococcus aureus, Pseudomonas aeruginosa and Clostridium difficile, (ii) prevention of pandemic influenza by appropriate pre-pandemic vaccination using vaccines with an established safety record, and (iii) vaccines for travellers to areas where there are diseases no longer present in the country of origin. There is thus a strong rationale for vaccines as the best insurance against the risks of diseases associated with modern society.

4. Vaccination for Low-Income Countries

Vaccines can also make a great contribution to reduction and possibly elimination of poverty from our planet. In developing countries, many vaccine-preventable diseases exact a huge toll on the income of families and throw them into a downward spiral of poverty [5–8]. Currently, five vaccines are recommended for routine use in developing countries. There is no established mechanism to develop those vaccines needed only in developing countries and for which there is no commercially viable market. Innovative mechanisms to make vaccines available to people in developing countries must be a priority in the twenty-first century for Western societies and for the governments of developing countries. Projects such as the Advanced Market Commitment, the Meningitis Vaccine Project and the Novartis Vaccines Institute for Global Health [6] are promising examples of initiatives that can help with funding, developing and deploying vaccines for the poorest people. In the coming years, the new technologies are going to offer very promising perspectives in the development of ‘unconventional’ vaccines, i.e. vaccines against non-infectious diseases (such as cancer, Alzheimer disease, diabetes, drug addiction, hypertension and autoimmune diseases), to expand the potential for vaccines to improve the quality of our lives. The potential of vaccines against cancer and chronic diseases is covered by the works of Liu [9] and Bachmann & Jennings [10]. In any case, concerted action, involving academic environments working in vaccine research and medical teaching, vaccine manufacturers, public health policy-makers and governments, will be needed if we want to eliminate poverty from our planet [11].

REFERENCES