

VACCINES: OUR INSURANCE FOR A HEALTHIER LIVING**R. Rappuoli****Novartis Vaccines and Diagnostics**

Abstract. In the 20th century, vaccination has been possibly the greatest revolution in health. Together with hygiene and antibiotics, vaccination led to the elimination of most childhood infectious diseases and contributed to prolong the disability-free life expectancy that in western societies increased from 50 to 78-85 years [1, 2]. In the 21st century, vaccination will 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 the aging society, 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; meningitis

THE NEED TO INCREASE PUBLIC CONFIDENCE IN VACCINATION

Up to very recently vaccines have been developed following the Pasteur example of inactivating and injecting the microorganisms causing the diseases ([3]. These primitive technologies, essentially developed during the first half of the 20th century, led to crude vaccine preparations that have been very successful in the conquest of diseases. However, they were often associated with some safety concerns. For instance, although it was instrumental for 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 due to vaccine-related autoimmune responses against the brain protein myelin [4]. Even the Sabin oral poliomyelitis vaccine, developed during the 1950s, was associated in one case per million with paralytic disease in vaccinees and contacts. Some of 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 20th 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 due to the perception that vaccines are great tools to fight fatal diseases but may be occasionally 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 paradoxical characteristic of a wealthy society. There is a false perception that some diseases are not or no longer dangerous. For example, many people consider measles as an entirely benign infection and

forget the high toll of morbidity and mortality it can cause at our latitudes. Measles epidemics do occur today in European countries due to rejection of vaccination and resulting in insufficient vaccination coverage. Similarly, there was a major epidemic of diphtheria in Russia due to disruption of the health system in former USSR and a reduced level of vaccination. This original sin vaccines are facing fostered the perception that vaccines are great but dangerous, and throughout the entire century people recurrently attributed to vaccination all those diseases of unknown cause. For instance, in the absence of a known cause of the raise of autism in the last decades, many people concluded that had to be caused by vaccination. First, they associated autism with measles, mumps and rubella vaccination. Then, when it was scientifically proven that this association was not there, others associated autism with the use of thimerosal, a mercury compound used until recently to preserve the sterility of vaccines [5]. Now, after the association of thimerosal with autism has been scientifically disproved, there are still some fundamentalists that refuse to accept the scientific evidence and insist that autism is caused by vaccination. Another example is the 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 [6], 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 Secession War, at a time when vaccines did not exist yet (except one). Another phenomenon that has happened during the last century is the increase of allergy in developed countries. Being of unknown cause, many have associated it with vaccination.

NEW TOOLS TO INCREASE PUBLIC CONFIDENCE

The perception that vaccination may be dangerous has been a major concern for vaccine developers and regu-

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Table 1. Vaccines associated with safety concerns that are no longer used

<i>Smallpox</i>	<i>generalized vaccinia, encephalitis, myocarditis</i>
<i>Sabin oral polio</i>	<i>paralytic disease in vaccinees and contacts</i>
<i>Measles high dose</i>	<i>increased mortality from all causes in females</i>
<i>Difteria Pertussis and Tetanus - DPT (whole cell Pertussis P)</i>	<i>febrile seizures and encephalopathy (disproved)</i>
<i>Rotavirus (Rotashield)</i>	<i>intersusception (bowel obstruction)</i>
<i>Bacillus Calmette-Guérin - BCG (tuberculosis)</i>	<i>disseminated BCG infection</i>
<i>Thimerosal</i>	<i>autism, neurodevelopmental delays (disproved)</i>

**Table 2.
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 immune response Th1/Th2
Profile of cytokines induced by novel adjuvants and vaccines to predict potential of autoimmunity, induction of expected immune response
Availability of well controlled cell lines to avoid 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 (brain extracts) 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, biomarker, immune response kinetics, efficacy, and safety
Mouse-human cross-over studies for understanding role of TLRs
Animal and in vitro models to test disease enhancement (RSV, influenza, measles)
Large phase III and phase IV studies to exclude statistically rare events

latory agencies that during the last 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, high dose measles, eccetera have been discontinued or are going to be discontinued soon (Table 1). Second, the new technologies allowed to minimize the risks associated with the new generation of vaccines. Highly purified components of known molecular entity, recombinant antigens, polysaccharides conjugated to purified proteins, new antigens discovered by genomics allowed the development of a new generation of molecularly tailored vaccines that are well characterized and intrinsically safer than the crude preparations of the 20th century. Live-attenuated vaccines that in the past were derived by random passages and mutagenesis today are 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 have been often a problem in the past. New tools that will continue to increase vaccine safety are listed in the enclosed Table 2.

However, elimination of the vaccines with safety concerns and minimization of the safety risks in present and future vaccines is not going to be enough to gain the public trust in vaccines. We need to educate people that, even in our rich countries, infectious diseases are still around us and that they are a real threat if our alert is discontinued and if a preventive 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 available in the 21st century. In other words, we need to remove from the mind of people the perception that vaccines are dangerous and are to be avoided, since this mindset is a relict of the 20th century and is not true any longer. In this respect, health policy makers should also actively pursue this perception starting from the consid-

eration that vaccination has contributed more than any other medical intervention in the reduction of human diseases.

21ST CENTURY VACCINES

Vaccines were developed in the 20th 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 vaccine success, the 21st century society lives longer and we should consider how vaccination can be redesigned to meet the needs of the health care systems that are struggling with the new reality.

Today vaccines address mostly infant diseases and we have >10 vaccines recommended in western countries for infant vaccination, one (papillomavirus) recommended in adolescent women and one (influenza) recommended in the elderly. In developing countries there are only 5 recommended vaccines, all for infants. However, thanks to the technology revolutions, genomics and the great progress in immunology, today it is possible to design vaccines able to prevent many diseases of modern society. For instance, we could think at a vaccination plan where before birth, pregnant women receive a boost vaccine during the third trimester to generate and transfer to the newborns antibodies against those diseases of the first few days or months of life, such as GBS, tetanus, hepatitis B, meningococcus, pneumococcus, RSV, influenza, using the strategy to protect newborns selected by nature during human evolution. Infants would then be vaccinated starting from 4-5 months of age to build their own active immunity. The next vaccination event would be in adolescents, who would receive those vaccines that prevent those chronic diseases and cancer associated with infectious diseases such as papillomavirus, which is associated with ovarian cancer, hepatitis C, which is associated with liver cancer, chlamydia which is associated with infertility, and those vaccines that would be useful during pregnancy such as CMV, GBS. Some vaccines like CMV and EBV have also the potential to slow the aging of the immune system, one of the major problems beyond the age of 50.

Finally, approximately at 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 modern aging society. These are resurging 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. 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* is a realistic goal. Prevention of pandemic influenza by appropriate pre-pandemic vaccination using vaccines with established safety record is a second one. Vaccines for travelers to areas with dis-

eases not longer present in the country of origin is a third one. In conclusion, there is strong rationale to propose vaccines as the best insurance against the risks of diseases associated with the modern society.

VACCINATION FOR LOW INCOME COUNTRIES

Vaccines can also make a great contribution to reduce and possibly eliminate poverty from our planet. In developing countries, many vaccine-preventable diseases exact a huge toll from the income of each family and throw them into a downward spiral of poverty [7-10]. Currently, five vaccines are recommended for routine use in developing countries, against >10 in western countries. In addition, there is no mechanism to develop those vaccines needed only in developing countries and for which there is no market. Innovative mechanisms to make vaccines available to the people in developing countries must be a priority in the 21st century for western societies and for the governments of development countries. Few projects such as the Advanced Market Commitment, the Meningitis Vaccine Project and the Novartis Vaccines Institute for Global Health [8] are a few promising examples of initiatives that can help funding, developing and deploying vaccines to the poorest people. The new technology is going to offer in the coming years very promising perspectives in the development of "unconventional" vaccines, i.e. vaccines against non infectious diseases (such as cancer, Alzheimer, diabetes, drug addiction, hypertension, autoimmune diseases, etc), to extend then the potential for vaccines to improve the quality of our lives. In any case, a concerted action, involving academic environments working in vaccine research and medical teaching, vaccine manufacturers, public health policy makers, governments, eccetera, will be needed if we want to eliminate poverty from our planet.

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