

# Two Hundred Twenty Years of Vaccination<sup>1</sup>

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The procedure we call vaccination started about 220 years ago when the physician and scientist Edward Jenner administered the cowpox virus (or perhaps what was really the horsepox virus) to protect against smallpox. Now vaccination is practiced in every corner of the earth and is protecting the majority of humanity.

A vaccine can be defined as a killed or weakened live pathogen, or a component of a pathogen (e.g., nucleic acid or protein), that when administered to a human or animal stimulates a protective response of the cells in the immune system. As stated in the first chapter of my *Vaccines* textbook, “The impact of vaccination on the health of the world’s people is hard to exaggerate. With the exception of safe water, no other modality has had such a major impact on mortality reduction and population growth” (Plotkin et al. 2017). Figure 1 lists most of the vaccines given to children or adults in various parts of the world. When I look at that list I reflect that when I was born in 1932 there were no vaccines routinely given to children.

Even before Jenner’s smallpox vaccine, it is thought that for hundreds of years people in Central Asia and China were practicing variolation, in which material from smallpox pustules was incised into skin or given by intranasal insufflation to protect against serious systemic smallpox, a deadly plague that killed about a third of those it infected. Voltaire wrote amusingly about it in his *Philosophical Letters*, mentioning that women from the Caucasus destined for the harem of the Turkish sultan were routinely variolated (Voltaire 1733). It was the wife of the British ambassador to Turkey, Lady Mary Montagu, who observed the variolation and introduced it into England through the royal court. But of course it was Jenner’s vaccine that conquered smallpox, first in Europe and North America, and then in the 20th century throughout the world (Plotkin et al. 2017).

Nothing much happened in the vaccine world until the 1880s and the work of Louis Pasteur. We all know about his invention of a rabies

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Diphtheria	Measles
Tetanus	Mumps
Pertussis	Rubella
Polio	Varicella
Hepatitis B	Pneumococcus
Hemophilus influenzae	Human papillomavirus
Rotavirus	Meningococcus A, C, W, Y
Hepatitis A	Influenza
Japanese encephalitis	Tick-borne encephalitis
	Zoster

FIGURE 1. Vaccines for children and adolescents now routinely given in different parts of the world.

vaccine, but his intellectual process is less known. First, he was an accomplished, well-respected scientist before he began work on vaccines. Second, he began to think about vaccines after an accident in the laboratory led to a crucial insight (Plotkin et al. 2017). A culture of a bacterial pathogen for chickens was left in his lab during a summer vacation. When he came back to the lab after vacation and tried to infect chickens with the culture, they did not die. He made a fresh culture and inoculated the same chickens, but again they did not die. Then the light bulb went on, and he realized that the chickens had been protected by the prior heat-inactivated culture. That observation was responsible for his famous subsequent work on vaccines against anthrax and rabies. The process he used was a form of attenuation, or weakening, of a pathogen.

The other major path toward vaccine development, inactivation or killing of pathogens, was actually first pursued by two Americans, Daniel Salmon and Theobald Smith, who developed chemical inactivation of bacteria (Plotkin et al. 2017). Figures 2 and 3 show the subsequent use of attenuation and inactivation that was necessary in order to develop the vaccines we have today.

I will illustrate the power of vaccination with five examples: rotavirus, human papillomavirus, meningococcal vaccines, Ebola vaccine, and maternal immunization. A rotavirus vaccine developed in my own laboratory was introduced to the United States in 2006 (Clark et al. 1996). Its effect was immediate, in that the incidence of diarrhea in infants, and specifically rotavirus diarrhea, dropped precipitously.

The vaccine against human papillomavirus has not reached its full potential owing to the prejudice that parents have about vaccinating against a sexually transmitted disease, but its efficacy is close to 100 percent, and it will eventually eliminate most cervical cancers, as well

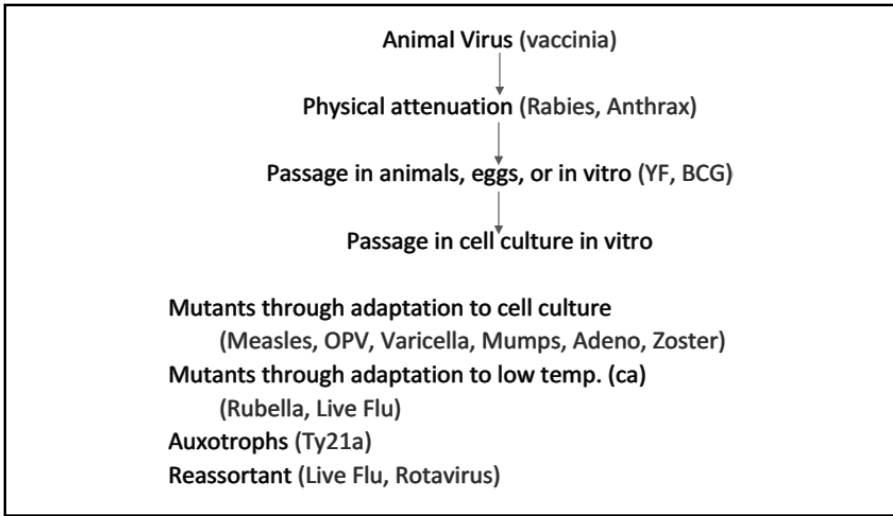


FIGURE 2. Attenuated vaccines.

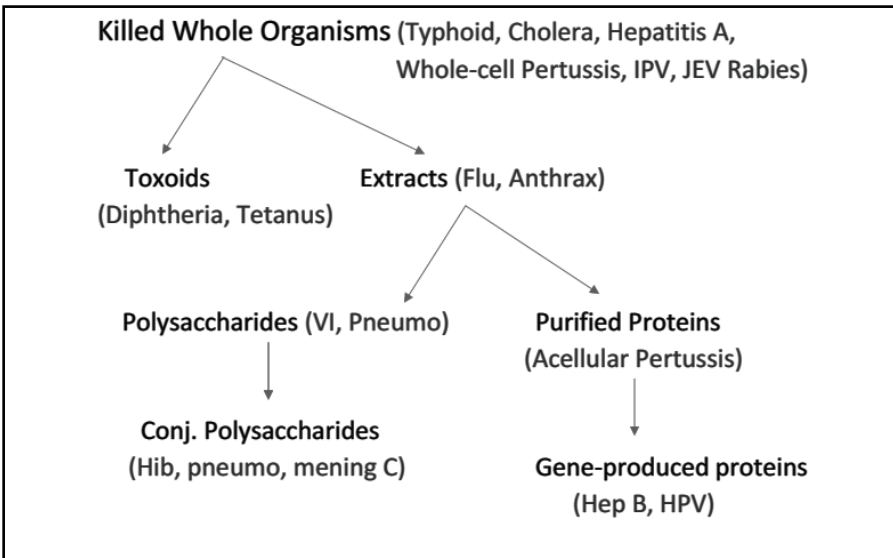


FIGURE 3. Inactivated vaccines.

as much oropharyngeal cancer in men (Ferris et al. 2014). In addition, an experimental vaccine has shown promise in causing regression of cervical cancers that have already developed (Trimble et al. 2015).

Meningococcal meningitis is a devastating disease with high fatality. Meningococcal group A vaccination is used routinely in countries like the United States to prevent sporadic cases, but in Africa, where the disease is epidemic, the vaccine has literally stopped the disease in its tracks, practically eliminating deaths due to the bacteria (Mustapha and Harrison 2018).

The story of Ebola in West Africa is well-known and frightening. Although unfortunately it took too long to bring a vaccine to Africa in order to control the disease, its introduction was a dramatic success. By 10 days after vaccination there were no more cases of Ebola, whereas a comparable unvaccinated population continued to have the disease (Henao-Restrepo et al. 2015).

Lastly, protection of newborns by vaccination is difficult because their immune systems are not well-developed. However, newborns may receive passive protection through the passage of antibodies from the mother through the placenta to the fetus. Therefore, pregnant mothers are now being given tetanus, pertussis, and influenza vaccines that will protect both themselves and their infants, who will have antibodies against those diseases for some months after birth (Fortner et al. 2018).

Whereas vaccines by and large have been very successful, some need improvements. For example, the old vaccine against pertussis was able to control the disease but caused significant reactions in children. Accordingly, so-called acellular vaccines were developed in the 1990s, which are virtually free of serious reactions. However, recent observations document that the acellular vaccines protect for much fewer years than do the prior cellular vaccines. Improvements on the acellular vaccines are under study, including the use of stronger adjuvants, additional proteins from the pertussis organism, and boosters with a live attenuated pertussis strain (Burdin, Handy, and Plotkin 2017).

Influenza vaccine is recommended for practically everybody, but clearly is often only partly effective because the virus is constantly mutating to escape immunity. Much work is being done to find ways to improve influenza vaccine effectiveness. Among the many projects aiming to augment efficacy is one that hopes to use a conserved part of the influenza virus surface hemagglutinin protein, which is in the stalk of the protein. There are only two stalks in influenza strains that infect humans, and the hope is that including those portions of the proteins in vaccines will broaden immune responses to cover mutating strains (Krammer and Palese 2013).

In 1902, Émile Roux, the successor to Pasteur as head of the Pasteur Institute, gave a talk during the inauguration of a monument to his predecessor. He said, “Science appears calm and triumphant when it is completed: but science in the process of being done is only contradiction and torment, hope and disappointment.” Any scientist will agree and understand that statement. In the field of vaccinology there have also been frustrations, which I will illustrate with the examples of respiratory syncytial virus (RSV), cytomegalovirus (CMV), and HIV.

Respiratory syncytial virus is the most important respiratory infection in children and the second most important in the elderly, after influenza. It has resisted vaccine development for many years despite efforts to use the so-called F protein of the virus as a vaccine, which for theoretical reasons should induce a protective response. Recently, using structural biology, it was demonstrated that the F protein exists in two forms, so-called prefusion and postfusion (Graham 2017). The latter is easy to produce and had been used in the failed attempts to show protection from RSV. However, the prefusion F is constructed differently and when presented to the immune system much stronger responses are elicited. Therefore, there are many current efforts to use prefusion F in a vaccine against respiratory syncytial virus.

The human cytomegalovirus is the most important virus most people have never heard of. CMV is the most frequent worldwide cause of congenital abnormalities including microcephaly, deafness, retinitis, and mental retardation; it is also the most common cause of disease and organ rejection in transplant patients. Attempts have been made to develop a vaccine since the 1970s, when I developed a vaccine candidate, but the results have been only partly successful. An important scientific advance now gives promise of success: the identification of a complex of five proteins on the surface of the virus. This pentamer, as it is called, is responsible for the induction of the majority of neutralizing antibodies and therefore will be crucial to include in a CMV vaccine (Schleiss, Permar, and Plotkin 2017).

As we all know, there is no vaccine against HIV, the cause of AIDS. This is because there is no natural immunity, which prevents us from inferring how to stimulate it by vaccination; because strain variation is extreme, worse than in the case of influenza; and because dissemination from the sexual mucosa takes place within 24 to 72 hours of exposure (Gao, McKay, and Mann 2018). Progress toward vaccine development has been slow, but several observations give hope. First, it appears possible to induce broadly neutralizing antibodies against the virus; second, an experimental vaccine gave about 30 percent protection; and third, non-neutralizing antibodies can also protect (Haynes

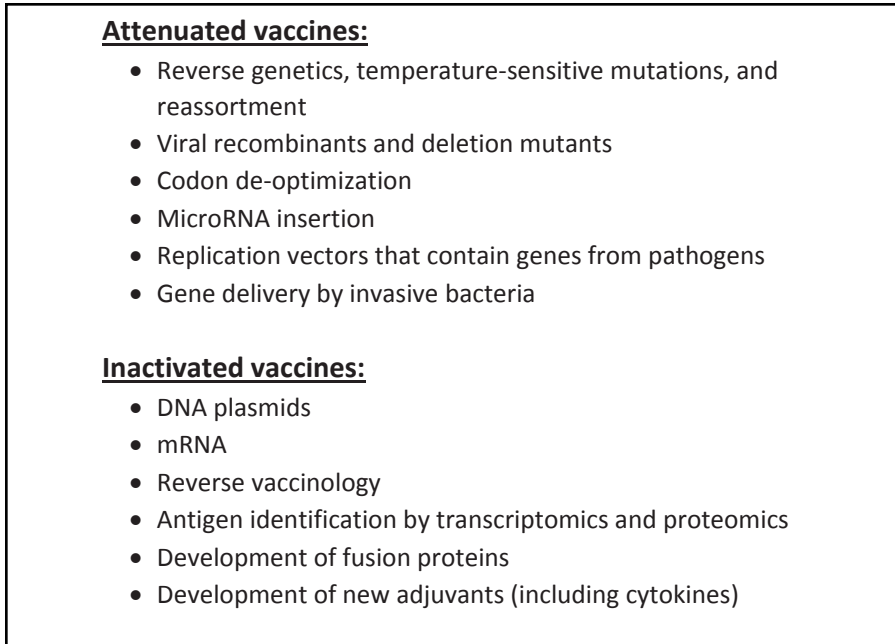


FIGURE 4. New strategies for vaccine discovery. Data from Plotkin and Plotkin (2011).

2015). At least two important trials of experimental vaccines are in progress.

The future of vaccine development is bright because a number of new strategies are promising, as listed in Figure 4. In particular, vaccines based on nucleic acids of organisms should provide ways to rapidly develop vaccines (Ferraro et al. 2011; Pardi et al. 2018). In addition, the world now has an approach to vaccine development for emerging diseases that have little commercial interest for large manufacturers. In 2015, with Jeremy Farrar of the Wellcome Trust and the late Adel Mahmoud, in response to the Ebola crisis I proposed the development of an international fund to carry vaccines from their conception in academic or government laboratories to development and licensure by industry (Plotkin, Mahmoud, and Farrar 2015). The new fund, called the Coalition for Epidemic Preparedness Innovations, now exists and is developing vaccines for diseases like Lassa, MERS, and Chikungunya (Plotkin 2017).

Despite the above advantages of vaccination, we must recognize the growing resistance to vaccines based on ignorance, fear, misconstrued risks, and lack of altruism, inasmuch as an immune population protects the immunodeficient. People should take the advice of Benjamin

Franklin, who lost his son to smallpox and regretted not having protected him by variolation. Franklin commented that parents who feared variolation should learn from his example, which showed that between having smallpox or variolation, “the regret may be either way, and that therefore the safer should be chosen.”

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