Vaccines and infectious diseases

What is a vaccine?

A vaccine is an immune system stimulator intended to elicit an immune response to a specific pathogen. In theory, the immune system of a vaccinated individual will be capable of mounting an immediate response when it is exposed to the actual pathogen, and the rapid immune response will either attenuate or completely prevent the deleterious consequences of infection.

Because, in extremely rare cases, the magnitude of the immune system response to the vaccine may be harmful or fatal to the individual vaccinated, and because, in rare cases, the vaccine may itself cause a disease, a small group of vocal people are opposed to vaccines. This opposition is exacerbated by the fact that vaccines are unusual in that they are given to healthy individuals. However, vaccines (in conjunction with other public health measures) have clearly played a major role in limiting and in some cases eradicating formerly lethal epidemic diseases from entire continents. Vaccines are partially responsible for removing infectious disease from its former location as the leading cause of death in industrialized countries.[4]

Historical aspects

Observations over the last few millenia suggested that, for many diseases, individuals who survived a specific disease became immune to later infection by the same disease. The ability to use this information was limited, however, by the fact that infecting an individual with a disease in order to prevent a later incidence of the same disease was not really a worthwhile solution.

For smallpox, the idea of giving the disease to uninfected individuals was actually used. The process of **variolation** (the term is derived from variola, the name of the smallpox virus) involved inoculating individuals with fluid from smallpox pustules of infected individuals. Variolation was dangerous, with more than 1% of the treated individuals dying as a result. However, smallpox had a 30% mortality rate. The danger associated with the variolation process resulted in a search for an improved method of protecting people from the smallpox epidemics that repeatedly swept through the population.

In the 18th century, milkmaids were rarely observed to develop smallpox. The folk wisdom was that this was because milkmaids associated with cows, and had contracted cowpox. In 1796 a country physician, Edward Jenner, decided to test this folk wisdom. Jenner injected cowpox virus (removed from the sores induced by cowpox) into an 8-year-old boy, James Phipps. A few weeks later, Jenner injected Phipps with smallpox, and found that Phipps did not develop the disease. Edward Jenner attempted to publish the results of his single trial in the scientific literature of the time; his paper was rejected, and he had to publish the results himself. Although it was not immediately obvious at the time, the development of the

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[4] In the US in 1999, heart disease killed 725,000, cancer killed 550,000, stroke killed 167,000, chronic respiratory diseases killed 124,000, accidents killed 98,000, and diabetes mellitus killed 68,000. In contrast, influenza and pneumonia combined killed 64,000, septicemia killed 31,000, and HIV killed 15,000. (Source: *Deaths: Final Data for 1999*, CDC, National Center for Health Statistics.)

smallpox vaccine was a major landmark in the history of medicine. Although smallpox probably killed 500 million people during the 20th century, the eventual effect of the smallpox vaccine was the complete eradication of smallpox. The last wild case of smallpox occurred in Somalia in 1977, and the last known case in humans (the result of a laboratory accident in Birmingham, England, occurred in 1978).

Viral diseases and the immune system

The immune system has two methods for dealing with a virus. One involves the use of antibodies that bind to the viral particles. These antibodies assist in clearing the virus, and in some cases, prevent viral particles from interacting with cells. The second method is for the immune system to kill the infected cell. Vaccines are designed to elicit an immune response. In general, unless cells from the host organism become infected by the vaccine, the immune response will be limited to antibody generation, and will not involve formation of the T-cells targeted to infected cells. Because the antibody-producing B-cells specific for the antigen tend to decrease in number over time, vaccines that do not involve some live organism tend to result in weaker immune responses, and tend to require booster administration of the vaccine at intervals (usually after 5 or 10 years).

Types of vaccines

Many types of vaccines have been used or are being evaluated for different diseases.

1. Live, non-pathogenic organism with similarities to the pathogen

This was historically the first type of vaccine. The cowpox and vaccinia viruses are similar to the variola virus, which causes smallpox. The similarities are such that an immune response against cowpox or vaccinia prevents an infection by the potentially lethal variola virus.

Following the success of the smallpox vaccine, the use of live non-pathogens as vaccines has been proposed for many infectious diseases. Unfortunately, the technique has not always been successful. For example, in the early 20th century the BCG (Bacille Calmette-Guérin) strain of *Mycobacterium bovis* was developed. The BCG strain was generated by selecting for an organism with limited pathogenicity in humans that was similar enough to *Mycobacterium tuberculosis* to elicit an immune response that would protect against tuberculosis. However, the technology for storing the cells did not exist until about 1960, so the cells have had to be maintained in culture since 1920. This lengthy interval has resulted in considerable variation in the properties of different samples of the BCG bacterium. The variability in the cells has also resulted in a variable response to vaccination with the cells, and many people vaccinated with BCG have not developed immunity to the pathogenic *M. tuberculosis*. In addition to the limited effectiveness as a vaccine against tuberculosis, some lots of BCG are somewhat pathogenic; this is a significant problem for immunocompromised individuals. The limited efficacy and mild hazard of the BCG vaccine have prevented the FDA from approving the vaccine for use in the US.

The BCG vaccine has one other drawback: exposure to BCG causes a positive response to the commonly used tuberculin test for tuberculosis, with the result that many people have been treated for a disease that they may not actually have.

The limited usefulness of the BCG vaccine points out some of the problems with using live non-pathogenic organisms: the organism used may not be entirely non-pathogenic, and may not be similar enough to the pathogen to successfully elicit a protective immune response.

2. Attenuated pathogen

An attenuated pathogen is a live virus that is unable to cause severe disease. In most cases, this has involved growing the virus in cells that do not allow normal replication of the virus, and selecting for viral strains that have lost pathogenic characteristics.

The Sabin polio vaccine is an example of a live attenuated virus.

The advantages of virus-based vaccines are that the virus replicates and therefore produces a larger and more varied immune response. In most cases, as with live, non-pathogenic vaccines, the resulting immunity is life-long. Attenuated pathogens (and live non-pathogens) also have the possibility of infecting individuals that have not been directly vaccinated with the modified pathogen, and therefore potentially protect a larger portion of the population.

On the other hand, attenuated pathogens occasionally reacquire pathogenicity, and therefore may cause disease. The Sabin vaccine causes non-infectious paralytic polio in about 1 in 750,000 vaccinated individuals. In extremely rare cases, the Sabin vaccine has been implicated in reformation of an infectious pathogen.

(Side note: HIV has been proposed to have arisen as a result of a polio vaccination program in central Africa. The hypothesis is that chimpanzee cells were used to propagate the virus used for the vaccinations. However, the individuals who ran the program have stated that monkey cells, not chimpanzee cells, were used. This contention is supported by data on similar samples, which contain monkey and not chimpanzee DNA[5]. In addition, evolutionary studies have suggested that HIV arose between 1914 and 1941, which is prior to the period during the mid-1950s in which the polio vaccination program was active.)

3. Dead pathogens

Pathogens can be inactivated by exposure to chemicals that denature their proteins or otherwise disrupt their structure. Injection of the inactivated pathogen can elicit an immune response, although the response tends to be both less powerful and shorter lasting than the response to live organisms. In most cases dead pathogen vaccines do not confer life long immunity, and therefore require periodic booster shots to maintain immunity. Assuming the inactivation process is complete, a dead pathogen vaccine therefore trades increased safety (in that it cannot cause disease) for lower efficacy.

The Salk polio vaccine is an inactivated pathogen vaccine. In industrialized countries where polio is rare, the Salk vaccine is preferred over the Sabin vaccine.

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[5] See *Science* **292**, 615 and 743-744 (2001)

Poorer countries, where polio is more prevalent, and where access to healthcare is limited, tend to prefer the Sabin vaccine because rapid public health responses to sudden outbreaks of the disease are unlikely.

Although killed pathogen vaccines are relatively safe, rare cases of the incomplete activation have resulted in the infection of people treated with the vaccine.

4. Subunits of pathogens

The methods listed above used "old-fashioned" chemistry and biochemistry to generate the vaccine. However, more recently, the tools of biotechnology have been applied to the generation of safer vaccines. Pathogen surface antigens (such as viral coat proteins) can be expressed in heterologous organisms such as *E. coli*. The proteins purified from these cultures have never been part of an active pathogen, and cannot cause disease. These recombinant protein vaccines are generally safer than the earlier vaccine types.

5. Recombinant viruses

While recombinant subunit vaccines are safe (with the exception of possible allergic responses or direct toxicity of the injected protein), they result in limited immune responses. One possible method of producing a vaccine is to create engineer a non-pathogenic virus by inserting genes for pathogen antigens. For example, vaccinia virus could be engineered to contain surface antigens from another virus or from a non-viral pathogen.

Engineering viruses is not a trivial undertaking. Vaccinia virus contains a large genome (187 kb). Unlike many viruses, vaccinia replicates in the cytoplasm of the infected cell. This is possible because vaccinia has genes for DNA and RNA polymerases and for the maturation of its mRNA, and therefore does not need the nuclear machinery of the host cell.

Vaccinia virus engineering requires homologous recombination because the large size of its genome prevents the use of many standard molecular biological techniques. (It also lacks unique restriction sites.) In addition, the engineered virus must be carefully tested to ensure that it is not pathogenic.[6]

6. Recombinant bacteria

An even newer technique involves the engineering of a bacterial strain to incorporate cell surface antigens from a pathogen. This method has not yet been used clinically, but it has been considered as a possible method for producing vaccines against bacterial and parasitic diseases.

Treatment of viral diseases

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[6] It had been thought that creating a pathogenic virus would be difficult. However, recently, a non-pathogenic virus was converted into a virulently lethal variant of the mousepox virus (capable of killing even vaccinated mice) by the addition of a single cytokine gene. This is the first case (at least in the open literature) of the use of molecular biology to create a deadly pathogen. Fortunately, the mousepox virus only affects mice, and a similar experiment using vaccinia virus did not produce a pathogen. For more information, see *Science* **291**, 585 (2001).

The general principle of a virus is very simple: infect a cell, and then use the cellular machinery to synthesize and release more viruses.

While bacteria and parasites contain large numbers of enzymes and other cellular machinery that offer potential targets for antibiotics, in general, viruses merely make use of existing cellular machinery. As a result, finding a drug that eliminates a virus without damaging the host cell (or the patient as a whole) has proven to be extremely difficult. Currently, curing a viral disease is impossible. The alternatives are to prevent the initial infection (with a vaccine) or to reduce (but not abolish) the rate of viral reproduction.

Anti-viral drugs must take advantage of viral enzymes that differ from normal host cell enzymes. This approach has been used to treat human immunodeficiency virus infection.

The HIV contains three enzymes: a reverse transcriptase, an integrase, and a protease. The reverse transcriptase is necessary to convert the retroviral RNA genome to DNA. The integrase catalyzes the insertion of the reverse transcribed genome into the genome of the host cell. The protease is required to cleave viral translation products into the mature active proteins. Crystal structures containing the active domains of all of the HIV enzymes have been solved; a combination of the structural information and extensive biochemical research has resulted in the development of inhibitors of both the reverse transcriptase and the protease, with integrase inhibitors currently in clinical trials. Unfortunately, the high rate of mutation of HIV and the fact that HIV is capable of producing latently infected cells that are not affected by the drugs have resulted in reductions but not eradication of the infections in nearly all of the individuals treated. The propensity for mutation has also prevented (at least thus far) the successful development of a protective vaccine against HIV.

Vaccination ethical issues

Unlike the vast majority of drugs, vaccines are used to treat healthy individuals. Although complication rates for most vaccines are very low, these complications occur in individuals who might never have been exposed to the disease. In some cases (*e.g.*, with attenuated pathogens), the vaccine may cause the disease it was designed to prevent. In addition, vaccines may have side effects (*e.g.*, an attenuated retrovirus would still incorporate its DNA into the host cell genome and that insertion event may have adverse consequences). These difficulties mean that risk-benefit ratios for the use of any vaccine must be considered carefully.

Other potential ethical issues with vaccines involve individual behavior. One type of behavior is avoiding vaccination on the assumption that the rest of the population will be vaccinated and will therefore prevent the exposure of the unvaccinated individual. This type of behavior involves an assessment of the relative risks of being vaccinated and of being exposed to the disease that is generally based on inadequate information.

A second type of behavior involves the assumption that the vaccine protects the individual against infection. While many vaccines do offer fairly complete protection, some vaccinated individuals may still be susceptible to the disease. The assumption of protection may result in unwillingness to avoid behavior associated with exposure to the disease and consequent infection.

A third potential ethical problem with vaccines is that humans have a tendency to assume that events occurring in temporal proximity have a common cause. This has meant that development of any abnormality in a recently vaccinated individual tends to be evaluated (at least by those individuals and their families) as being caused by the vaccine. In the United States, adverse effects that might be associated with commercial products result in lawsuits. The result of frequent litigation is that profits for making vaccines tend to be extremely small. Convincing pharmaceutical companies to spend the hundreds of millions of dollars necessary to develop new vaccines has become increasingly difficult, and some companies that have produced vaccines in the past no longer do so in order to avoid the controversy and expense of lawsuits.

