Immunotherapy and immunoprophylaxis – passive and active immunity

Introduction

The human immune system provides protection against foreign antigens, many of which take the form of infectious agents such as bacteria, viruses, parasites and fungi. However, until the body has been exposed to an organism, it has to rely on innate immune responses for protection. Once exposed to an organism, the adaptive immune system is able to form a specific immune response and form memory cells able to respond more rapidly to future exposure to the organism.

The timing however is not always convenient – for protection, the individual needs to have an immune response ready before exposure, as exposure to the organism may result in disease. By exposing an individual to a harmless form of the organism's antigens, a similar immune response can be elicited without risk of disease resulting from a true infection. This is what occurs during active immunisation or vaccination – vaccines are non-pathogenic forms of the organism or its antigens. The result is ideally a combination of cellular and humoral immune responses that mimic those that occur with a natural infection. The aim is to produce either sterilising immunity (protection against infection by neutralising the organism before it can spread in the body) or protective immunity (protection against disease by halting the infection before pathology or symptoms develop).

Specific immunity can also be transferred to an individual without that individual developing an adaptive memory response. This occurs naturally when antibodies are transferred across the placenta from a mother to her child, and in clinical practice it can occur artificially by injecting antibodies into an individual. Passive transfer of cellular immunity is not routinely practised; however, HLA-compatible T-cells, including T-cells from the individual that have been stimulated in vitro, have been transfused into patients to provide an immune response against organisms or tumours.

Clinical uses for vaccines

Pre-exposure prophylaxis – vaccines taken before exposure may prevent infection or disease when the person is exposed to the wildtype virus.

Post-exposure prophylaxis – after exposure, vaccination may stimulate a more rapid immune response, providing protection. For detailed examples, see the sections on hepatitis B and rabies, as well as the section on post-exposure prophylaxis.

Therapy – therapeutic viral vaccines are still experimental, but scientists are interested in the potential effects on HIV progression.

Passive immunisation

Passive immunity is transferred from mother to child across the placenta, providing immunity for the first months of life. For the same reason, testing for IgG in infants may merely indicate maternal IgG, and not an acquired immunity in the infant. Also, response to certain vaccines may be sub-optimal as a result of these antibodies.

Historically, the first antibodies to be used clinically were against tetanus and diphtheria in 1890. During World War II, plasma protein fractionation was used to separate out antibodies, and eventually organism-specific antibodies could be separated from the rest. Viral infections were initially often treated with antibodies. Today antibodies – either normal human immunoglobulin (total immunoglobulin) or hyperimmune globulin (organism-specific) – are still an important part of prophylaxis against certain viral infections such as hepatitis A, hepatitis B, rabies, measles, varicella and respiratory syncytial virus (RSV). In the modern era of laboratory-synthesised monoclonal antibodies, RSV can be prevented with palivizumab, a recombinant human-mouse monoclonal, and monoclonal antibodies for other viruses, such as foravirumab and rafivirumab for rabies, are in development. Passive immunity has also shown some effect in preventing mortality in cases of Ebola.

Active immunisation

Vaccines are biological substances that are used to induce or improve immunity to a specific disease. The word vaccine comes from the Latin word for cow, i.e. *vacca*, via the Latin for *cowpox*, which Edward Jenner used to make his smallpox vaccine in 1796. Vaccines can be prophylactic (preventing disease) or therapeutic (ameliorating disease.) Therapeutic and preventative HIV vaccines are currently in clinical trials.

History of vaccines

Variolation, the practice of infecting people with low doses of smallpox, dates back to 1000 BC in India. It would generally induce a mild form of the disease, which would prevent the person from being re-infected. Edward Jenner realised that a milkmaid infected with cowpox would not subsequently get smallpox. Cowpox caused a mild infection, and so the first live vaccine was found. Later it was discovered that the virus being used for smallpox vaccination (Fig. 1) was in fact vaccinia, not cowpox, albeit related. Louis Pasteur (Fig. 2) went further with this process and developed the first rabies vaccine.

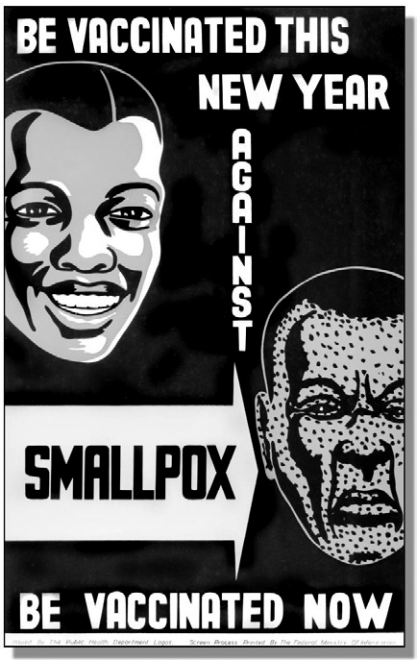

Fig. 1 **Advertisement for the smallpox vaccine.** (Photo courtesy of CDC/Stafford Smith.)

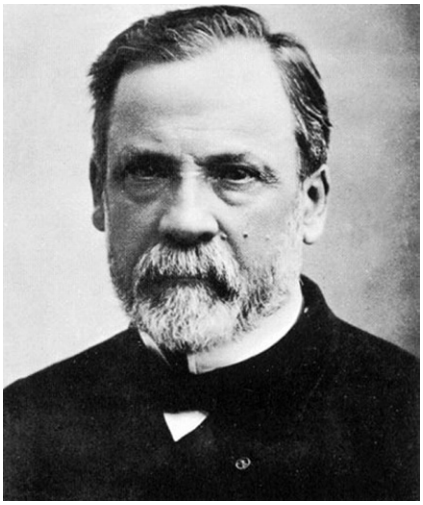

Fig. 2 **Louis Pasteur (1822–1895)** taken in 1878 by Gaspard-Félix Tournachon.

Types of vaccines

Several types of vaccines, and potential vaccines, exist, ranging from live organisms to DNA that results in the production of certain proteins made by the organism. See Table 1 for examples:

Live attenuated vaccines – a virus is passaged many times in a cell line, and this results in attenuation of the virus. Most live attenuated viruses carry little risk of serious infection, with the smallpox vaccine being the notable exception. Measles, varicella, oral polio and yellow fever vaccines may rarely induce complications similar to that of the wildtype virus.

Inactivated vaccines – wildtype viruses can be inactivated, usually with formaldehyde or a similar chemical, and thereafter no longer cause disease, although a protective immune response can still be formed against the virus.

Split vaccines – after inactivation of the viruses, the killed viruses are disrupted by detergents and used for vaccination.

Subunit vaccines – after inactivation of the viruses, killed viruses are then split into their many components and certain components are separated from the rest for use in the vaccine.

Recombinant vaccines – if a specific viral antigen or set of viral antigens can be identified, the genes for those antigens can be inserted into other organisms, e.g. brewer's yeast (*Saccharomyces cerevisiae*) in the case of hepatitis B surface antigen. In the case of human papillomavirus vaccines, virus-like particles (VLPs) are produced without any genome present, which means that they cannot replicate.

Table 1 **Types of vaccines and examples of each**

Viral vaccines			
LAV	***Whole killed***	***Subunit***	***Recombinant***
Varicella	Hepatitis A	Influenza	Hepatitis B
Measles		Hepatitis B†	HPV: VLPs
Mumps	Polio (IPV)		
Rubella	Rabies		
Polio (OPV)	Japanese encephalitis B		
Yellow fever	Tick-borne encephalitis		
Influenza (nasal)	Influenza		
Rotavirus	RVF*		
Smallpox*			

*Not publicly available; †limited availability. HPV, human papilloma virus; RVF, Rift Valley fever; VLP, virus-like particles; IPV, inactivated polio vaccine; OPV, oral polio vaccine.

Fig. 3 **Children lined up for their vaccines.** (Photo courtesy of CDC.)

Toxoid vaccines – if an organism produces a toxin, this toxin can be inactivated (thereby becoming a toxoid), and may still induce immunity that is protective against the toxin itself. No viral toxoid vaccines are available.

DNA vaccines – naked DNA may be injected, or delivered in other ways, into the skin or muscle. This DNA is taken up by the cells, and the proteins it codes for may be produced. Immunity against viral proteins can be induced in this way. No DNA vaccines are currently available commercially.

Vector vaccines – these are live but harmless viruses (or bacteria) that carry genes for other viruses, and are able to produce some of the proteins made by the harmful virus without risk of infection from those viruses. The vector vaccines may or may not be able to replicate completely in the host. Research into HIV vaccines has used vectors such as MVA (modified vaccinia Ankara) and canarypox.

Adjuvants – adjuvants are substances that enhance an immune response to a foreign protein. Without an adjuvant, the immune response may be weak or temporary, but the addition of an adjuvant may strengthen the response, or permit memory cells to form. Examples are aluminium compounds, liposomes and even capsid proteins from *Neisseria meningitidis*.

Development

A lot of research goes into vaccine development each year, as many new vaccines are needed by the world, especially against malaria and HIV, and safer vaccines against TB are needed in the era of HIV infection. Influenza vaccines are different each year, due to changing circulating strains and new influenza antigens need to be determined for both northern and southern hemispheres.

Vaccine schedules

Countries often have a recommended list of vaccines that they advise their citizens to have. For some, it is compulsory for children to have certain vaccines at certain ages, although few countries do not respect the rights of the parents to decline vaccination. In many cases, vaccines are supplied free of charge by the government's health system (Fig. 3).