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Immunity and how vaccines work

Introduction

Immunity is the ability of the human body to protect itself from infectious disease. The defence mechanisms of the body are complex and include innate (non-specific, non-adaptive) mechanisms and acquired (specific, adaptive) systems.

Innate or non-specific immunity is present from birth and includes physical barriers (e.g. intact skin and mucous membranes), chemical barriers (e.g. gastric acid, digestive enzymes and bacteriostatic fatty acids of the skin), phagocytic cells and the complement system.

Acquired immunity is generally specific to a single organism or to a group of closely related organisms. There are two basic mechanisms for acquiring immunity – active and passive.

Active immunity

Active immunity is protection that is produced by an individual's own immune system and is usually long-lasting. Such immunity generally involves cellular responses, serum antibodies or a combination acting against one or more antigens on the infecting organism. Active immunity can be acquired by natural disease or by vaccination. Vaccines generally provide immunity similar to that provided by the natural infection, but without the risk from the disease or its complications. Active immunity can be divided into antibody-mediated and cell-mediated components.

Antibody-mediated immunity

Antibody-mediated responses are produced by B lymphocytes (or B cells), and their direct descendants, known as plasma cells. When a B cell encounters an antigen that it recognises, the B cell is stimulated to proliferate and produce large numbers of lymphocytes secreting an antibody to this antigen. Replication and differentiation of B cells into plasma cells is regulated by contact with the antigen and by interactions with T cells (a type of lymphocyte), macrophages and complement. The antibody provides immunity against infection in a variety of ways. These ways include neutralising toxins, blocking adhesion and cell entry by organisms, neutralising and preventing viral replication or complement-mediated killing.

Cell-mediated immunity

Cell-mediated immunity is controlled by a subset of lymphocytes called T lymphocytes or T cells. T cells mediate three principal functions: help, suppression and cytotoxicity. T-helper cells stimulate the immune response of other cells (i.e. T cells stimulate B cells to produce antibodies). T-suppressor cells play an inhibitory role and control the level and quality of the immune response. Cytotoxic T cells recognise and destroy infected cells and activate phagocytes to destroy pathogens they have taken up.

These two components of specific immunity are closely related to each other, and T cells interact with B cells in the production of antibodies against most antigens. Specific antibodies and cell-mediated responses are induced for all infections, but the magnitude and quality of these two components vary in different infections.

Passive immunity

Passive immunity is protection provided from the transfer of antibodies from immune individuals, most commonly across the placenta or less often from the transfusion of blood or blood products including immunoglobulin. Protection provided by the cross-placental transfer of antibodies from mother to child is more effective against some infections (e.g. tetanus and measles) than for others (e.g. polio and whooping cough). This protection is temporary – commonly for only a few weeks or months.

How vaccines work

Vaccines produce their protective effect by inducing active immunity and providing immunological memory. Immunological memory enables the immune system to recognise and respond rapidly to exposure to natural infection at a later date and thus to prevent or modify the disease. Antibodies can be detected in blood or serum or other body fluids, but, even in the absence of detectable antibodies, immunological memory may still be present. Cell- mediated responses to some vaccines (e.g. BCG, see Chapter 32) may be detectable by skin testing but do not necessarily indicate protection.

Traditional vaccines are made from whole pathogens, either inactivated (killed) or attenuated live organisms, secreted products including toxins or parts of the pathogen's structure either as viral like particles or subunit vaccines.

Newer vaccines are being developed and produced using recombinant viral vectors to deliver the antigen (Ewer *et al.* 2016). These viral vectors can either be replicating vectors where there is local replication and hence amplification in the recipient, analogous to the live attenuated vaccines, or non-replicating vectors or replication deficient vectors, that can only replicate in certain cell lines used for manufacture, and more analogous to the inactivated vaccines

The newest types of vaccine use the pathogen's genetic code as the vaccine; this then exploits the host cell's apparatus (including enzymes and ribosomes) to translate the proteins that then act as an intracellular antigen and stimulate the immune response (van Riel and de Wit, 2020). These DNA or RNA vaccines often use a lipid outer shell to aid entry into the cell, and may have modified nucleotides or nucleosides to delay degradation by host cell machinery and to modulate the correct components of the immune system (Verbeke *et al* 2019). In some of these vaccines the genetic sequence can code for self-replication within the host cell to produce even more antigen and therefore induce a more robust response. mRNA is a natural component of the body, does not enter the nucleus and is processed entirely in the cytoplasm. Any mRNA that is not taken into cells is rapidly degraded by circulating ribonucleases. DNA vaccines enter the nucleus where mRNA is produced by the host cells RNA polymerase. The mRNA then passes into the cells cytoplasm to be translated into protein. DNA vaccines do not integrate into host cell DNA and are degraded by normal cellular processes.

Vaccines such as inactivated poliomyelitis virus (IPV) contain inactivated bacteria or viruses. Other vaccines contain only the antigens that are important for protection. For example, tetanus and diphtheria vaccines contain inactivated toxins (toxoids), influenza vaccine contains a surface protein called haemagglutinin, and pneumococcal vaccine contains the polysaccharide from the capsule. Live attenuated vaccines include yellow fever; measles, mumps and rubella (MMR); and BCG.

From birth and in early infancy and childhood, humans are exposed to countless numbers of foreign antigens and infectious agents in the everyday environment. Responding to these stimuli helps the immune system to develop and mature. Compared with exposure in the natural environment, vaccines provide specific stimulation to a small number of antigens. Responding to these specific antigens uses only a tiny proportion of the capacity of an infant's immune system (Offit *et al.*, 2002). If an infant's immune system could be exhausted by multiple vaccines, one would expect vaccinated children to be at a higher risk of serious infections. Studies to investigate whether vaccines increase susceptibility to serious infections have shown no evidence of such an effect, with infection rates generally being lower in vaccinated children (Hviid *et al.*, 2005, Miller *et al.*, 2003).

Inactivated vaccines/non-replicating or replication deficient vaccines

A first injection of an inactivated vaccine or toxoid in an individual without prior exposure to the antigen produces a primary antibody response. This response is dominated by IgM antibody initially, followed by IgG antibody. Two or more injections may be needed to elicit such a response in young infants. This is usually called the primary course. Depending on the potency of the product and the time interval, further injections will lead to an accelerated response dominated by IgG – the secondary response. Following a primary course of vaccination, antibodies may persist for months or years. Even if the level of detectable antibody subsequently falls, the immune system has been primed and an individual may be protected. Further reinforcing doses of vaccine are used to boost immunity and to provide longer-term protection. Inactivated vaccines cannot cause the disease that they are designed to prevent.

Plain polysaccharide antigens do not stimulate the immune system as broadly as protein antigens such as tetanus, diphtheria or influenza. Therefore, protection from such vaccines is not long-lasting and response in infants and young children is poor. Some polysaccharide vaccines have been enhanced by conjugation – where the polysaccharide antigen is attached to a protein carrier (e.g. Hib, PCV and MenACWY vaccines). This enables the immune system to respond more broadly to the antigen to provide immunological memory, even in young children. Some inactivated vaccines contain adjuvants, substances that enhance the antibody response. Most combination vaccines contain adjuvants such as aluminium phosphate or aluminium hydroxide.

Live vaccines/replicating vaccines

Live attenuated virus vaccines, such as MMR, usually promote a full, long-lasting antibody response after one or two doses. To produce an immune response, the live organism must replicate (grow) in the vaccinated individual over a period of time (days or weeks). The immune system responds in the same way as it does to natural infection. It usually does this without causing the disease itself (because the vaccine virus is weakened or 'attenuated') but, for some vaccines, a mild form of the disease may rarely occur (e.g. a rash following measles-containing vaccines).

Replicating vector vaccines generally use vector pathogens that are naturally of low pathogenicity and have key genetic components, including the genes for the viral vectors structural proteins removed.

Vaccine failure

No vaccine offers 100% protection and a proportion of individuals get infected despite vaccination. Vaccines can fail in two main ways – known as primary or secondary vaccine failures. Primary failure occurs when an individual fails to make an initial immunological response to the vaccine. Infection can therefore occur at any point after vaccination. A good example of primary vaccine failure is the 5–10% of children who do not respond to the measles component of the first dose of MMR. The risk of measles in such children is reduced by offering an additional dose of vaccine, usually before school entry.

Secondary failure occurs when an individual responds initially but then protection wanes over time. The incidence of secondary vaccine failure therefore increases with time.

Individuals who acquire infection despite vaccination may have a modified, milder form of disease and are less likely to suffer serious complications than those who have never been vaccinated. An example of secondary vaccine failure is pertussis vaccine, when protection against whooping cough after three doses is initially high but declines as a child gets older. A fourth (booster) dose is given to improve protection during the school years.

How are vaccines made

Vaccines are usually made by growing cultures of the target virus or bacterium. Viruses need to grow in cells and so vaccine viruses are often grown in eggs (e.g. influenza) or in cell-lines derived from mammals, including humans. This culture media provides numerous nutritious elements and growth factors that may have been obtained from materials of animal origin, such as serum, milk and milk derivatives, gelatine, meat extract or extracts from other muscular tissues. These components are used in the early stages of the manufacturing and should not be present, or only be present in trace amounts (residues) in the final vaccines.

Animal enzymes are also used during the manufacture of vaccine viruses but subsequent washing, purification and dilution steps removes them from the final vaccine. One example is trypsin, normally derived from pigs, which is widely used during the manufacture of vaccines, usually being added to the final cell culture to activate the vaccine virus. Trypsin is also used during the manufacture of other medical products e.g. insulin and heparin. The trypsin is then eliminated during the next steps of the manufacturing process (for example by washing and filtration).

What cell lines are used for vaccines

The mammalian cell lines used to grow the virus for a vaccine will normally derive from a primary culture of cells from an organ of a single animal which has then been propagated repeatedly in the laboratory, often over many decades. For example, measles vaccine is grown in chick embryo cells and polio vaccines are grown in a mouse cell line. Another animal cell line, now being used to make egg-free flu vaccine, was derived in 1958 from the kidney of a cocker spaniel.

The best-known human cell line is MRC5; these cells derive from the lung of a 14-week-old male fetus from a pregnancy that was terminated for medical reasons in 1966. This cell-line is used to grow viruses for vaccines against rubella, chickenpox and hepatitis A. Other fetal cell lines have been used for other vaccines, including influenza and some of the new COVID-19 vaccines. No fetal material is present in the final vaccine. The moral issues around the use of vaccines grown on fetal cell lines have been discussed within the Catholic church. The church distinguishes between the ethics of the initial termination, but states that acceptance of such vaccines where there is no appropriate alternative does not signify cooperation with abortion.

www.academyforlife.va/content/pav/en/the-academy/activity-academy/note-vaccini.html

Recombinant protein vaccines are usually also expressed in cell lines but these are less commonly of mammalian origin and may use insect cells and bacteria. For example, hepatitis B vaccine is expressed in yeast and human papillomavirus vaccine in insect cells. Vaccines based on genetic material are an exception in that the DNA or RNA can be synthesised chemically. However, for some of these vaccines, cell-lines may be required earlier in the production process and products such as enzymes and stabiliser may still be important.

What do vaccines contain?

As vaccines are generally complex biological products, a number of substances are used to ensure the quality of the final product. These substances perform an important function in ensuring the vaccine is safe and effective and are classified as excipients. Constituents that are intended to be in the final product, are listed on the SmPC. Further information on commonly used vaccine ingredients can be found on these public websites.

<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/common-ingredients-us-licensed-vaccines>

<http://vk.ovg.ox.ac.uk/vk/vaccine-ingredients>

Highly processed derivatives of animal materials are occasionally used, in the finished vaccine product and are classified as excipients. Gelatine is an example of an animal product used in a very wide range of medicines, including many capsules and some vaccines. Gelatine is used in vaccines as a stabiliser – to ensure that the vaccine remains safe and effective during storage. Unlike the gelatine used in foods, the product used in vaccines is highly purified and broken down into very small molecules called peptides. The presence of porcine gelatine in vaccines has raised issues around acceptability to some faith groups which is discussed in this leaflet.

<https://www.gov.uk/government/publications/vaccines-and-porcine-gelatine>

Some really important chemicals – called adjuvants – are used to improve the immune response to vaccines. The most commonly used adjuvants are aluminium salts. Aluminium salts, such as aluminium hydroxide, aluminium phosphate, and aluminium potassium sulphate have been used safely in vaccines for more than 70 years. Aluminium salts were initially tested in the 1930s-1950s with diphtheria and tetanus vaccines and it was shown that they improved the immune response to these vaccines by ensuring that the vaccine remains at the site of injection to be taken up by the cells of the immune system. They are thought to be particularly effective at stimulating humoral immunity (Brewer, 2006). Research has shown the amount

of aluminium exposure in people who follow the recommended vaccine schedule is low and is not readily absorbed by the body. (Mitkus *et al*, 2011)

Newer adjuvants have been now developed to target specific components of the immune response, so that protection against disease is stronger and lasts longer. Many of these are based on lipids, and one example is MF59. This adjuvant is derived from "squalene" an oil that is extracted from the shark's liver. This adjuvant is used in the influenza vaccine that is given to the elderly in this country where it improves the level of protection against influenza. Similar adjuvants are being considered for some of the COVID-19 vaccines.

Population immunity

The primary aim of vaccination is to protect the individual who receives the vaccine. Vaccinated individuals are also less likely to be a source of infection to others. This reduces the risk of unvaccinated individuals being exposed to infection. This means that individuals who cannot be vaccinated will still benefit from the routine vaccination programme. This concept is called population (or 'herd') immunity. For example, infants below the age of one year, are no longer routinely immunised against serogroup C meningococcal infection. Such babies are protected from meningococcal infection because teenagers have been routinely immunised with MenACWY conjugate vaccine. Young adults normally have the highest rate of nasopharyngeal carriage of meningococci but by vaccinating teenagers in year 10 at school, the carriage rate is reduced and so is transmission to all members of the population.

When vaccine coverage is high enough to induce high levels of population immunity, infections may even be eliminated from the country or region, e.g. poliomyelitis. But if high vaccination coverage is not maintained, it would be possible for the disease to return. Vaccination against smallpox enabled the infection to be declared eradicated from the world in 1980. The World Health Organization (WHO) is currently close to the goal of the global eradication of poliomyelitis.

Immunoglobulins

Passive immunity can be provided by the injection of human immunoglobulin which contains antibodies to the target infection and temporarily increases an individual's antibody level to that specific infection. Protection is afforded within a few days but may last only a few weeks.

Human normal immunoglobulin (HNIG) is derived from the pooled plasma of donors and contains antibodies to infectious agents that are currently prevalent in the general population. HNIG is used for the protection of immunocompromised children exposed to measles and of individuals after exposure to hepatitis A.

Specific immunoglobulins are available for tetanus, hepatitis B, rabies and varicella zoster. Each specific immunoglobulin contains antibodies against the target infection at a higher titre than that present in normal immunoglobulin. Specific immunoglobulins are obtained from the pooled blood of donors who:

- are convalescing from the target infectious disease, or
- have been recently immunised with the relevant vaccine, or
- are found on screening to have sufficiently high antibody titres

Recommendations for the use of normal and specific immunoglobulins are given in the relevant chapters.

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