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Immunology and Vaccine-Preventable Diseases

To understand how vaccines work and the foundation of recommendations for their use, it is helpful to understand the basic function of the human immune system. The following description is simplified; many excellent immunology textbooks provide additional detail.

Immunity is the ability of the human body to tolerate the presence of material indigenous to the body and to eliminate foreign substances. This discriminatory ability to eliminate foreign substances is performed by a complex system of interacting cells called the immune system. Since most organisms (e.g., bacteria, viruses, and fungi) are identified as foreign, the ability to identify and eliminate these substances provides protection from infectious diseases. Immunity is generally specific to a single organism or group of closely related organisms.

The immune system develops a defense against antigens, which are substances that can stimulate the immune system. This defense is known as the immune response and usually involves the production of:

- Protein molecules (immunoglobulins or antibodies, the major component of humoral immunity) by B-lymphocytes (B-cells)
- Specific cells, including T-lymphocytes (also known as cell-mediated immunity)

The most effective immune responses are generally produced in response to antigens present in a live organism. However, an antigen does not necessarily have to be present in a live organism to produce an immune response. Some antigens, such as hepatitis B surface antigen, are easily recognized by the immune system and produce adequate protection even if they are not carried on the live hepatitis B virus. Other materials are less effective antigens, and the immune response they produce may not provide good protection.

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Types of Immunity

There are two basic mechanisms for acquiring immunity: passive and active.

Passive Immunity

Passive immunity is protection by antibody or antitoxin produced by one animal or human and transferred to another. Passive immunity provides immediate protection against infection, but that protection is temporary. The antibodies will degrade during a period of weeks to months, and the recipient will no longer be protected.

The most common form of passive immunity is that which an infant receives from the mother. Antibodies, specifically the class of antibody referred to as IgG, are transported across the placenta, primarily during the last 1 to 2 months of pregnancy. As a result, a full-term infant will have the same type of antibodies as the mother. These antibodies can protect the infant from certain diseases within the first few months after birth. Maternal antibodies provide better protection from some diseases (e.g., measles, rubella, tetanus) than from others (e.g., polio, pertussis).

Passive immunity can also be acquired through the transfusion of blood products. Some blood products (e.g., washed or reconstituted red blood cells) contain a relatively small amount of antibody, while some (e.g., intravenous immune globulin and plasma products) contain a large amount.

In addition to blood products used for transfusion, there are three other major sources of antibody used in human medicine. These are homologous pooled human antibody, homologous human hyperimmune globulin, and heterologous hyperimmune serum.

Homologous pooled human antibody, also known as immune globulin, is produced by combining the antibody fraction, specifically the class of antibody referred to as IgG, from the blood of thousands of adult donors. Because it comes from many different donors, it contains antibody to many different antigens. It is used primarily for prophylaxis for hepatitis A and measles, and treatment of certain congenital immunoglobulin deficiencies.

Homologous human hyperimmune globulins are antibody products that contain high titers of antibody targeting more specific antigens. These products are made from donated human plasma with high levels of the antibody of interest. Since hyperimmune globulins are from humans, they are primarily polyclonal, containing many types of antibodies in lesser quantities. Hyperimmune globulins are used for postexposure prophylaxis for several diseases, including hepatitis B, rabies, tetanus, and varicella.

Heterologous hyperimmune serum, also known as antitoxin, is produced in animals, usually horses, and contains antibodies against only one antigen. In the United States, antitoxins are available for the treatment of botulism and diphtheria. These products can cause serum sickness, an immune reaction to the horse protein.

Immune globulin products from human sources are primarily polyclonal; they contain many kinds of antibodies. Monoclonal antibody products have many applications, including the diagnosis of certain types of cancer (colorectal, prostate, ovarian, breast), treatment of cancer (B-cell chronic lymphocytic leukemia, non-Hodgkin lymphoma), prevention of transplant rejection, and treatment of autoimmune (Crohn's disease, rheumatoid arthritis) and infectious diseases.

While certain antibody products, such as immune globulins, interfere with the immune response to live-virus vaccines, monoclonal antibody products do not because they are directed against one antigen or a closely related group of antigens. A monoclonal antibody product, palivizumab (Synagis), is available for the prevention of respiratory syncytial virus (RSV) infection. Since Synagis only contains RSV antibody, it will not interfere with the response to a live vaccine.

Active Immunity

Active immunity is protection produced by a person's own immune system. The immune system is stimulated by an antigen to produce antibody-mediated and cell-mediated immunity. Unlike passive immunity, which is temporary, active immunity usually lasts for many years, often for a lifetime.

One way to acquire active immunity is to survive infection with the disease-causing form of the organism. In general, once persons recover from infectious diseases, they will have lifelong immunity to that disease (there are exceptions, e.g., malaria). The persistence of protection for many years after the infection is known as immunologic memory. Following exposure of the immune system to an antigen, certain memory B-cells continue to circulate in the blood and reside in the bone marrow for many years. Upon re-exposure to the antigen, these memory

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cells begin to replicate and produce antibody rapidly to reestablish protection.

Another way to produce active immunity is by vaccination. Vaccines contain antigens that stimulate the immune system to produce an immune response that is often similar to that produced by the natural infection. With vaccination, however, the recipient is not subjected to the disease and its potential complications.

Many factors may influence the immune response to vaccination. These include the presence of maternal antibody, the nature and dose of antigen, the route of administration, and the presence of an adjuvant (e.g., aluminum-containing material added to improve immunogenicity of the vaccine). Host factors, such as age, nutrition, genetics, and coexisting disease, may also affect the immune response. The more similar a vaccine is to the disease-causing form of the organism, the better the immune response to the vaccine.

Classification of Vaccines

There are two basic types of vaccines. Their characteristics are different and determine how each type is used.

1. Live, attenuated, and
2. Inactivated.

Live, Attenuated Vaccines

Live vaccines are derived from "wild" viruses or bacteria. These wild viruses or bacteria are attenuated (weakened) in a laboratory, usually by repeated culturing. For example, the measles virus used as a vaccine today was isolated from a child with measles disease in 1954. Almost 10 years of serial passage using tissue culture media were required to transform the wild virus into the attenuated vaccine virus.

To produce an immune response, live, attenuated vaccines must replicate in the vaccinated person. A relatively small dose of administered virus or bacteria replicates in the body and creates enough of the organism to stimulate an immune response.

Although live, attenuated vaccines replicate, they usually do not cause disease such as that caused by the wild form of the organism. When a live, attenuated vaccine does cause disease, it is usually much milder than the natural disease and is considered an adverse reaction to the vaccine.

The immune response to a live, attenuated vaccine is virtually identical to that produced by a natural infection because the immune system does not differentiate between an infection with a weakened vaccine virus and an infection with a wild

virus. Injected live, attenuated vaccines produce immunity in most recipients with one dose. However, a small percentage of recipients do not respond to the first dose of an injected live, attenuated vaccine (such as measles, mumps, and rubella [MMR]) and a second dose is recommended to provide an extremely high level of immunity in the population. Orally administered live, attenuated vaccines require more than one dose to produce immunity.

A live, attenuated vaccine may cause severe or fatal infections as a result of uncontrolled replication of the vaccine virus or bacteria. However, this only occurs in persons with a weakened immune system (e.g., from leukemia, treatment with certain drugs, or human immunodeficiency virus [HIV] infection).

A live, attenuated vaccine virus could theoretically revert to its original pathogenic form. This is known to happen only with live (oral) polio vaccine, which is no longer available in the United States.

Active immunity from a live, attenuated vaccine may not develop because of interference with the vaccine virus by circulating antibody. Antibody from any source (e.g., transplacental transfer to infants, transfusion of blood products) can interfere with replication of the vaccine organism and lead to poor response or no response to the vaccine (also known as vaccine failure).

Live, attenuated vaccines are fragile and can be damaged or destroyed by heat and light. They must be stored and handled carefully. The live, attenuated viral vaccines currently available and routinely recommended in the United States are MMR, varicella, rotavirus, and influenza (intranasal). Other non-routinely recommended live vaccines include adenovirus vaccine (used by the military), typhoid vaccine (Ty21a), and Bacille Calmette-Guerin (BCG). BCG is not used as a vaccine in the United States, but as a treatment for bladder cancer.

Inactivated Vaccines

Inactivated vaccines are not live and cannot replicate. These vaccines cannot cause disease, even in an immunodeficient person. Inactivated antigens are less affected by circulating antibody than are live antigens, so they may be given when antibody is present in the blood (e.g., in infancy or following receipt of antibody-containing blood products).

The immunity provided by inactivated vaccines is generally not as long-lasting as that obtained from live, attenuated vaccines. Multiple doses over time are needed to obtain ongoing immunity. In general, the first dose does not produce protective immunity, but "primes" the immune system. A protective

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immune response develops after the second or third dose. Unlike live vaccines, which produce an immune response that closely resembles natural infection, the immune response to an inactivated vaccine is mostly antibody production. Little or no cellular immunity results. Antibody titers against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost," antibody titers.

Inactivated vaccines include whole-cell inactivated vaccines (e.g., polio, hepatitis A, and rabies vaccines), subunit vaccines (e.g., influenza and pneumococcal vaccines), toxoids (e.g., diphtheria and tetanus toxoid), and recombinant vaccines (e.g., hepatitis B, human papillomavirus [HPV], and influenza [Flublok brand]).

Whole-cell inactivated vaccines contain bacteria or viruses that have been killed through a physical or chemical process. Whole-cell inactivated viral vaccines against polio, hepatitis A, and rabies are available in the United States. A vaccine made from whole killed pertussis (whooping cough) bacteria is available outside the United States.

Subunit vaccines contain a portion of the bacteria or virus. The portion of the organism selected is the part needed to produce a protective immune response. Antigens in subunit vaccines can be protein, polysaccharide, or a combination of polysaccharide and protein molecule (i.e., conjugate vaccine).

Conjugate subunit vaccines (e.g., *Haemophilus influenzae* type b and pneumococcal conjugate vaccines) are produced by chemically attaching a polysaccharide from the surface of bacteria to a protein molecule through a process called conjugation. Conjugating a polysaccharide antigen to a protein molecule produces long-lasting protective immunity to the polysaccharide antigen.

The immune response to a pure polysaccharide vaccine is typically T-cell-independent, which means these vaccines can stimulate B-cells without the assistance of T-helper cells. T-cell-independent antigens, including polysaccharide vaccines, are not consistently immunogenic in children younger than age 2 years, probably because of immaturity of the immune system. Attaching the polysaccharide antigen to a protein makes it possible to prevent bacterial infections in populations where a polysaccharide vaccine is not effective or provides only temporary protection.

Toxoid vaccines are made using inactivated toxins produced by bacteria. These protein-based toxins are inactivated using heat, chemicals, or other methods. Some bacteria (e.g., tetanus, diphtheria) cause disease by producing toxins. The ability of the immune system to recognize and eliminate these toxins provides protection from the disease.

Recombinant vaccines are produced by recombinant DNA technology. Recombinant DNA technology enables the combination of DNA from two or more sources. Hepatitis B, human papillomavirus (HPV), and influenza (Flublok brand) vaccines are produced by insertion of a segment of the respective viral gene into the gene of a yeast cell or virus. The modified yeast cell or virus produces pure hepatitis B surface antigen, HPV capsid protein, or influenza hemagglutinin when it grows. Serogroup B meningococcal vaccines are proteins and outer membrane vesicles generated by recombinant technology.

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