Immunoprophylaxis of infectious diseases

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Prophylaxis of infectious diseases represents the actions taken before or shortly upon exposure of an individual to an infectious agent or its product (e.g. toxin), aimed to prevent infection and disease development. The most important prophylactic method is **immunoprophylaxis** in which a process of **immunization** is used for preventing infections. The goal of immunization is to induce immunity (i.e. state of resistance to an infection) in an immunized person for a certain period of time (that may vary from several weeks to several decades).

Immunization can be achieved spontaneously without any intentional human activity (called **natural immunization**) or by a deliberate action of men (so-called **artificial immunization**), and both of them can be actively induced in an individual by exposure to a pathogen or its components or products (**active immunization**) or passively adopted through immunoglobulin transfer (**passive immunization).** Natural immunity is actively induced after each infection, whereas the neonatal protection by maternal antibodies transported across the placenta to the fetus (IgG) and via immunoglobulins in milk (breast feeding - predominantly IgA) is an example of natural passive immunization. On the other hand, **artificial active immunization** is most commonly done by exposure of an individual to nonpathogenic forms or microbes or their components and/or products, a process called **vaccination**, while **artificial passive immunization** represents the induction of immunity through administration of human immunoglobulins or animal sera specific for the pathogen or its toxins. In the text that follows, these two forms of immunization performed by medical workers will be described in more details.

PASSIVE IMMUNIZATION

Artificial passive immunization is mediated by the administration of antibodies of human or animal origin to an individual. These products have **immediate action**, but induce **short-lived immunity** that lasts weeks to several months, which is determined by the half-life of immunoglobulins (around three weeks for IgG and only few days for the other isotypes).

In general, passive immunization is used for **prophylactic purposes**, to protect immunodeficient patients (prematurely born children or patients with defects in humoral immunity) against various infections or to prevent disease development after exposure of an individual to a particular pathogen (for example, after accidental injury by the HBV-contaminated needle or bite by the animals infected by rabies virus). However, in some cases, passive immunization (owing to its immediate action) can also be used for **therapy** with the aim to reduce the clinical symptoms of the disease and often represents the life-saving therapeutic method. For example, it is used for toxin-mediated diseases such as diphtheria

and botulism, or when the person is exposed to some toxins from animals, such as snake venoms.

Passive immunity is most commonly induced by the administration of human immunoglobulins, but animal sera and monoclonal antibodies are also sometimes used for the passive immunization of individuals.

The immunoglobulins of human origin contain primarily IgG antibodies extracted from the plasma of great number of blood donors and usually are given via intravenous or intramuscular routes of administration. Depending on the method of production and the purpose of their application, two groups of products are available:

- **Human serum globulin** (**gammaglobulin** or **intravenous immunoglobulins**, **IVIG**) contains antibodies that are specific for various pathogens that are commonly encountered by the majority of people and are present in the blood of most adults (the normal repertoire of antibodies in human population). They are extracted from the plasma of thousands of randomly selected blood donors. These products are used for the prophylaxis of infectious diseases in patients with a deficit in antibody production (hypo- or agammaglobulinemia). Also, they are sometimes used for prevention of specific infectious diseases (e.g. measles, hepatitis A, rubella in the first trimester of pregnancy etc.) in cases when the products with high titer of specific immunolgobulins (see below) are not available. In addition to prevention of infectious disease, intravenous immunoglobulins (IVIG) are also being increasingly used for haematological diseases (for example, idiopathic thrombocytopenia, ITP) and various autoimmune diseases.
- **Specific immunoglobulins** or **high-titer immunoglobulins** (also called **hyperimmune globulins**) contain high titer of antibodies specific for particular pathogen and they are used in the prophylaxis or therapy for specific infectious disease. They are extracted from the plasma of seropositive people with high-titer antibodies for a certain pathogen, i.e. those who were vaccinated or recently suffered from the disease caused by that pathogen. These products have been developed for hepatitis B, tetanus, rabies, respiratory syncytial virus (RSV), varicella (chickenpox) and other pathogens/diseases...

Apart from human immunoglobulins, animal sera are also sometimes used for passive immunization. **Animal sera** are obtained from animals (usually horses) immunized with specific antigen (mostly toxin of interest) and contain animal immunoglobulins specific for that antigen (such sera are called **antisera** or **antitoxins**). Animal proteins, including horse immunoglobulins, usually induce strong humoral response in humans, which may lead to a formation of circulating immune complexes and their deposition in kidney and other organs and cause serum disease (type III hypersensitivity). Therefore, human immunoglobulins are used always when it is possible. However, in cases when production of human preparations is not convenient and human products are not available (e.g. against snake venoms or botulinum toxin), horse antisera are still used to block the toxicity of animal venoms or in therapy of some diseases, such as botulism.

Finally, **monoclonal antibodies** that are being increasingly used for the treatment of autoimmune and chronic inflammatory diseases can also be used for the prophylaxis or therapy of specific infectious diseases. For example, monoclonal antibodies are occasionally used for prevention of RSV infection in prematurely born children.

ACTIVE IMMUNIZATION (VACCINATION)

Vaccination is the most commonly used form of artificial immunization aimed to **actively induce** protective immune response against a certain pathogen in an individual and, in the event of subsequent exposure to that pathogen, prevent disease development in an immunized person. The term **vaccine** is derived from the Latin word *vacca* (cow), given that the first recorded successful vaccination of a child against smallpox (Edward Jenner, 1796) was carried out using vaccinia virus that causes cowpox. Since then, the development of many efficient vaccines against various pathogens has led to the striking decrease in the incidence of many common infectious diseases in the last 50 years. Moreover, the only human disease that has been eradicated by human intervention was smallpox, and this was achieved by a worldwide program of vaccination. Therefore, vaccination is considered to be one of the greatest successes of immunology and medicine in general. Unfortunately, occasional interruptions of vaccination programs in developing countries and in regions of social conflicts, as well as the increasing anti-vaccination movement have led to a local reemergence of some infectious diseases and represent constant threat to public health today.

As previously noted, vaccination is based on the principle of an exposure of an individual to a pathogen or its components and/or products, that are modified in a way that they can induce an immune response in vaccinated persons, but not the disease. The aim of vaccination is to **induce pathogen-specific adaptive immune response** that results in **immunological memory** through the generation of **memory T and B cells** and **long-lived plasma cells**. Since days or even weeks are needed for the development of memory cells, the vaccines are **not efficient right after their administration** (contrary to immunoglobulins that have immediate action), but they induce **long-lasting immunity** (usually for years and sometimes life-long protection). The majority of vaccines induce **T-cell dependent humoral immune response** and a production of **high-affinity antibodies**. These antibodies can neutralize or block pathogen binding to host cells or activate some of the effector mechanisms, such as the complement system. On the other hand, most vaccines are unable to induce strong cellular response mediated by $CD8^+$ cytotoxic T lymphocytes (CTLs), probably because exogenous proteins that enter the cell through endocytosis are not efficiently presented by class I MHC molecules. Still, some vaccines (mainly live, attenuated viral vaccines) induce good **cytotoxic response** in addition to T-dependant humoral response, while some other vaccines, such as polysaccharide vaccines against pneumococci and meningococci, induce **T-cell independent humoral immune response** to bacterial capsular polysaccharides.

Although vaccines are usually administered before exposure to pathogen (for **prophylactic purposes**), in some cases, when the incubation of disease is long enough, post-exposure vaccine administration is possible, too (rabies vaccine can be given soon after the infected animal bite and still be effective). Also, post-exposure administration can be efficient when given in combination with specific immunoglobulins (e.g. after accidental injury by the HBV-contaminated needle or protection against tetanus in non-vaccinated persons). As for the vaccine administration, the most common route of administration is **parenteral** (using subcutaneous or intramuscular injections), although mucosal (**oral** and **nasal**) vaccines that induce local production of protective IgA antibodies have been developed (e.g. Sabin oral polio vaccine and nasal flu vaccine).

Each vaccine must meet certain criteria in order to be suitable for the widespread use (Characteristics of high-quality vaccines are shown in Table 1). First of all, it has to be efficient (i.e. able to induce a protective immune response in the vast majority of vaccinated subjects) and safe (it should not cause disease or serious adverse effects). Next, good vaccines should induce both humoral and cell-mediated immunity (i.e. to activate CTLs), which is particularly important for the intracellular pathogens residing in cytosol. Also, it is important that the vaccine should induce a long-lasting immunity, thereby avoiding or reducing to a minimum the need for its re-application (booster doses). Finally, the vaccine has to fulfill certain practical requirements, such as stability (so that it can be easily transported and last for longer periods), ease of application (advantage of oral and nasal administration in comparison to injection), low price (vaccines should be available in developing countries), etc.

In general, vaccines that contain one or few antigens of a pathogen, such as subunit vaccines (see below), are associated with less adverse effects compared with whole-cell vaccines, but are less immunogenic (i.e. induce weaker immune response). There are two ways for overcoming this disadvantage, either by adding **adjuvants** that increase the immunogenicity of the vaccines or by **revaccination** (administration of several additional doses, so called **booster doses**, over a longer period of time). Adjuvants are believed to stimulate innate immunity by acting on dendritic cells and other antigen-presenting cells, through their accumulation, increased expression of costimulators and production of cytokines, which all results in activation of adaptive immunity to antigens present in vaccines. Adjuvants may also cause side effects, such as inflammation at the site of inoculation, but are rarely associated with more serious adverse events.

Finally, vaccines provide protection not only for the vaccinated people, but also for unvaccinated ones, if the majority of people in the population have been vaccinated, a phenomenon called **herd immunity** (also called herd effect, community immunity, or population immunity). It is a form of indirect protection from infectious disease that occurs when a large percentage of a population has become immune to an infection, thereby providing protection for individuals who are not immune. In other words, widespread vaccination reduces the number of susceptible people in the population, disrupts the transmission of infection and diminishes the probability for susceptible individuals to be exposed to a pathogen and develop disease.

Table 1. **Characteristics of high-quality vaccines**

Characteristic	***Explanation***
Safety	Vaccine must not cause disease or serious side effects
Efficacy of protection	Vaccine has to provide protection against disease after exposure to pathogen in majority of people
Sustained protection	Protection against disease must last for several years
Induction of neutralizing antibodies	Provides neutralization of toxins and their harmful effects
Induction of cytotoxic T cell response	Intracellular pathogens are more effectively eliminated by CTL
Practical considerations	Low cost, stability, ease of application (e.g. oral vaccine) etc.

Types of vaccines, their properties and mechanisms of action

All vaccines can be divided, based on their properties, into several groups or **types**: live, inactivated, subunit, conjugated and combined vaccines (Features of different vaccine types are presented in Table 2).

Live vaccines

Live vaccines are composed of viable microorganisms with limited capacity to induce disease in humans. These strains of pathogens usually infect other animal species (e.g. cow in case of smallpox vaccine) or their virulence has been reduced through a process called attenuation (so called attenuated strains), so these vaccines are also called **attenuated vaccines**.

Attenuation is usually performed by repeated pathogen passage in cell cultures in the absence of host immune mechanisms under conditions that are different from those present in human body (e.g. on lower temperature or in animal cells which normally cannot be infected by that pathogen). During that process, the accumulation of mutations and the adaptation of a pathogen to such new conditions results in a loss of its capacity to induce disease in humans. Recently, new approach of attenuation has been introduced based on genetic manipulation of a pathogen with the goal to induce mutations in genes coding for important virulence factors of that pathogen. Most vaccines against viral diseases belong to a group of live (attenuated) vaccines, such as vaccines against mumps, measles, rubella, chickenpox and polio (oral Sabin polio vaccine), as well as some vaccines against bacterial infections (e.g. BCG vaccine against tuberculosis, containing attenuated strain of *Mycobacterium bovis*). Special type of live vaccines is that obtained by **genetic recombination** or **reassortment** of homologous gene segments between the related viruses (e.g. vaccine for rotavirus that is made by genetic reassortment between human and bovine rotavirus).

In general, live vaccines are safe and provide **complete immune response** since they induce not only production of neutralizing and other antibodies but also T cell-mediated response (both CTLs and helper T cells). They also provide **long-lasting immunity**, so they are usually administered in one or two doses. Most of these vaccines are given to children in the second year of life (with the exception of BCG that is given at birth), because of the immunological immaturity of the infants and the presence of the maternal antibodies that can reduce immunogenicity of the vaccine and inhibit immune response of the host and consequently reduce efficacy of live vaccines. Live vaccines have certain limitations: they are **relatively unstable**, especially on the higher temperatures (that is why the transport and storage of these vaccines are complicated, especially in rural regions) and there is the **risk of causing disease** if given to **people with immunodeficiencies**. Therefore, live vaccines are not generally given to immunocompromised patients and pregnant women (for them, inactivated and subunit vaccines, although less effective, are safer choice).

Inactivated vaccines

Inactivated vaccines (also called **killed vaccines**) contain whole microorganisms that were killed using various chemicals (e.g. formaldehyde) or high temperatures, but their antigenic properties and immunogenicity were preserved. These vaccines are usually used for preventing disease where pathogen cannot be successfully attenuated. Inactivated vaccines

are **stable** and **safe** (except for the people allergic to vaccine components, e.g. egg) and they act mainly through **induction of antibodies** and are less potent in activation of CTLs. On the other hand, inactivated vaccines are less immunogenic than attenuated ones, so they are usually **administered with adjuvants** in more than one dose (frequent revaccination). Vaccines for whooping cough (pertussis), typhoid fever, polio (Salk vaccine) and influenza are examples of inactivated vaccines. Although inactivated vaccines are good and efficient, there is a tendency for these vaccines to be replaced by subunit vaccines (when they are available).

Subunit vaccines

Subunit vaccines represent a special form of inactivated vaccines. They are composed of structural components of microorganisms or their products (e.g. toxins) that can induce protective immune response in recipients, which is mediated primarily by **antibodies, mainly neutralizing**. Since they are composed of individual antigens, these vaccines are also called **antigenic vaccines**. Those antigens are obtained by **isolation and purification** of pathogen products, or, more often, by using **recombinant DNA techniques** (as recombinant proteins produced by yeast cells). They are typically **surface antigens**, mainly proteins, which are important for the adherence of virus or bacteria to host cells, or polysaccharide antigens in the capsules of encapsulated bacteria. Examples of such subunit vaccine are the vaccines against influenza (containing hemagglutinin and neuraminidase) and polysaccharide vaccines against pneumococci and meningococci.

Subunit vaccines also include vaccines against diseases mediated by toxins, such as diphtheria and tetanus. These vaccines do not contain bacteria that cause disease, but inactivated forms of their toxins, called **toxoids**. Toxoids are chemically modified in order to lose their toxicity, while keeping their antigenic properties and immunogenicity. Acellular pertussis vaccine contains both toxoid (modified pertussis toxin) and one or more surface antigen(s) of bacteria that cause whooping cough.

Hepatitis B (HBV) and human papilloma virus (HPV) vaccines represent the special type of subunit vaccines. They contain recombinant proteins (HbsAg of HBV and L1 protein of HPV) that tend to spontaneously associate and form **virus-like particles (VLP)**, which are not infectious (nucleic acid is not present), but are more immunogenic than the isolated proteins themselves.

Subunit vaccines are **stable** and **safe** (especially those that contain recombinant proteins), but due to their **low immunogenicity**, they have to be administered **with adjuvants** and in several doses (some subunit vaccines, such as HBV and HPV vaccines, can sometimes be administered without adjuvants, because of their increased immunogenicity).

Conjugated vaccines

Conjugated vaccines, a special type of subunit vaccines, have been recently developed as result of our better understanding of the process of T cell-B cell cooperation in which $CD4^+$ helper T cells stimulate B cells to produce high-affinity antibodies in T-dependent humoral immune response.

Typically, conjugated vaccines are those against encapsulated bacteria, such as pneumococci, meningococci and *Haemophilus influenzae* type B (HiB). The important virulence factor of these bacteria are capsules rich in polysaccharides, that enable them to avoid phagocytosis. The main mechanism of the host in defense against encapsulated

bacteria is T-independent humoral immune response mediated by B cells subsets in the spleen and mucosal organs (marginal zone B cells and B-1 cells, respectively). Unfortunately, children up to two years of age and patients without a spleen (splenectomized patients) are often unable to establish adequate humoral response to T-independent antigens and they are at increased risk to develop severe infections caused by these bacteria, such as meningitis and sepsis that are associated with high mortality and serious sequels. Therefore the existing subunit polysaccharide-containing vaccines are insufficiently efficient against those bacteria in young children and splenectomized individuals.

This limitation of polysaccharide vaccines has been overcome by the development of conjugated vaccines in which **capsular polysaccharides** of encapsulated bacteria (as T-independent antigen) are **chemically linked (conjugated)** to a protein that is T-dependent antigen (similar to hapten-carrier conjugates). Usually, **diphtheria toxoid** is used as protein component, due to the fact that children respond well to that antigen and there is long experience supporting its safety. In this way, T cell help is provided, not only to B cells specific for diphtheria toxoid, but also to polysaccharide-specific B cells. As a result, immunologic memory is induced and **high-affinity polysaccharide-specific antibodies** (mainly of IgG isotype) are produced, which are able to prevent severe infections caused by encapsulated bacteria in susceptible persons.

In general, conjugated vaccines have the same properties as other subunit vaccines, they are **safe** and are administered in several doses during the first two years of life (pneumoccocal and HiB vaccines) or later (meningococal vaccine). They are also recommended for all individuals without functional spleen. **Relatively high price** is their only shortcoming, which limits their use in developing countries.

Combined vaccines

Combined (or **combination**) **vaccines** are also called **polyvalent vaccines** (vaccines that contain only one antigen sometimes are called monovalent), since they contain several **antigens of different serotypes** of the same pathogen or a number of antigens from **different pathogens**. Examples for the first are above mentioned vaccines against pneumococci, i.e. polysaccharide vaccine that contain antigens of 23 the most common serotypes in population, or conjugated vaccine containing antigens of 10 or 13 serotypes that cause severe invasive infections in children. Examples for the second are DTP vaccine against diphtheria, tetanus and pertussis or combined live vaccine MMR against measles, mumps and rubella.

Combined vaccines have all good properties of single vaccines and it has been shown that they induce protective immune response to each component in the vaccine in the same magnitude as single vaccines do. Therefore, they are **very convenient** (less applications, lower price, fewer visits of a doctor etc.) and in a pediatric population there is a tendency to replace single vaccines with combined ones (new vaccines that contain five or more different pathogens are in use today).

Table 2. **Features of different vaccine types**

Type of vaccine	***Examples***	***Immunization principle***	***Form of protection***	***Advantages***	***Limitations***
Live (Attenuated)	Measles Mumps Rubella Varicela Polio (Sabin) Tuberculosis (BCG)	Weakened (attenuated) pathogen	Antibody production Cell-mediated immune response	Complete immune response Long-lasting immunity	Instability Risk in immunocompromised persons
Inactivated (Killed)	Influenza Polio (Salk) Pertussis	Killed (inactivated) pathogen	Antibody production	Stability Safety	Low immunogenicity (adjuvants) Shorter immunity (booster administration)
Subunit (Antigenic)	Diphteria Tetanus	Modified toxin (toxoid)			
	HBV	Recombinant antigen			
	Influenza	Purified antigens (H and N)			
Conjugated	Pneumococci Meningococci *Haemophilus influenzae* type B	Capsular polysaccharide linked to a protein (toxoid)	Antibody production (T-dependent humoral response)		
Combined (Polyvalent)	Pneumococci	Different serotypes of the same pathogen	As in single vaccines	As in single vaccines Very practical	As in single vaccines
	DTP MMR	Different pathogens			

BCG – Bacillus ”Calmette-Guerin“, attenuated strain of *Mycobacterium bovis*; HBV – Hepatitis B virus; HBsAg – surface antigen of HBV; H – Hemagglutinin; N – Neuraminidase; DTP – Diphteria, Tetanus, Pertussis; MMR – Measles, Mumps, Rubella.