Viral Vaccines

Because few drugs are useful against viral infections, prevention of infection by the use of vaccines is very important. Prevention of viral diseases can be achieved by the use of vaccines that induce active immunity or by the administration of preformed antibody that provides passive immunity.

Immunity to viral infection is based on the development of an immune response to specific antigens located on the surface of virus particles or virus-infected cells. For enveloped viruses, the important antigens are the surface glycoproteins.

The pathogenesis of a particular viral infection influences the objectives of immunoprophylaxis. Three major sites for viral replication

1) **Mucosal surfaces of respiratory tract and GI tract. Rhino; myxo; corona; parainfluenza; respiratory syncytial; rota**
2) **Infection at mucosal surfaces followed by spread systemically via blood and/or neurons to target organs: picorna; measles; mumps; HSV; varicella; hepatitis A and B.**
3) **Direct infection of blood stream via needle or bites and then spread to target organs: hepatitis B; flavi; bunya; rhabdo.**

Note:Local immunity via IgA very important in 1 and 2.

Certain characteristics of a virus or of a viral disease may complicate the generation of an effective vaccine.

1. The existence of many serotypes, as with rhinoviruses, and of large numbers of antigenic variants in animal reservoirs, as with influenza virus, makes vaccine production difficult.

2. The integration of viral DNA into host chromosomal DNA (retroviruses) and infection of cells of the host's immune system (HIV).

Active Immunity

There are two types of vaccines that induce **active** immunity: those that contain **live virus** whose pathogenicity has been **attenuated**[1] and those that contain **killed virus.** Some vaccines, such as the hepatitis B vaccine, contain purified viral proteins and are often called **subunit** vaccines. The features of subunit vaccines resemble those of killed vaccines because no viral replication occurs in these vaccines. The features of live and killed vaccines are listed in Table –1.

Table –1 Characteristics of Live and Killed Viral Vaccines		
Characteristic Number of doses	**Live Vaccine** **Singe**	**Killed vaccine** **multiple**
Duration of immunity	Longer	Shorter
Effectiveness of protection	Greater	Lower
Immunoglobulins produced	IgA[1] and IgG	IgG
Cell-mediated immunity produced	Yes	Weakly or none
Interruption of transmission of virulent virus	More effective	Less effective
Reversion to virulence	Possible	No
Stability at room temperature	Low	High
Excretion of vaccine virus and transmission to nonimmune contacts	Possible	No

[1]If the vaccine is given by the natural route.

In general, live vaccines are preferred to vaccines containing killed virus because their protection is **greater** and **longer-lasting.**

With live vaccines, the virus multiplies in the host, producing a prolonged antigenic stimulus, and both IgA and IgG are elicited when the vaccine is administered by the natural route of infection, e.g., when polio vaccine is given orally.

Although live vaccines stimulate a long-lasting response, booster doses are now recommended with measles and polio vaccines.

One unique form of a live, attenuated viral vaccine is the influenza vaccine that contains a **temperature-sensitive** mutant of the virus as the immunogen. The temperature-sensitive mutant will replicate in the cooler air passages of the nose, where it induces IgA-based immunity, whereas it will not replicate in the warmer lung tissue and therefore will not cause disease.

Advantage of Attenuated live-virus vaccines
1. Acting more like the natural infection with regard to their effect on immunity.
2.They multiply in the host and tend to stimulate longer-lasting antibody production,
3. Induce a good cell-mediated response.
4. Induce antibody production at the portal of entry.

There are four concerns about the use of live vaccines (disadvantage):

1. They are composed of attenuated viral mutants, which can **revert to virulence** either during vaccine production or in the immunized person. Reversion to virulence during production can be detected by quality control testing, but there is no test to predict whether reversion will occur in the immunized individual. Of the commonly used live vaccines, only polio vaccine has had problems regarding revertants; measles, mumps, rubella, and varicella vaccines have not.

   Even if the virus in the live vaccine does not revert, it can still cause disease because, although attenuated (weakened), it can still be pathogenic in a host with reduced immunity. For this reason, live viral vaccines should *not* be given to immunocompromised people or to pregnant women because the fetus may become infected.

2. The live vaccine can be **excreted** by the immunized person. This is a double-edged sword. It is advantageous if the spread of the virus successfully immunizes others, as occurs with the live polio vaccine. However, it could be a problem if, e.g., a virulent poliovirus revertant spreads to a susceptible person. Rare cases of paralytic polio occur in the United States each year by this route of infection.
3. A second virus could **contaminate** the vaccine if it was present in the cell cultures used to prepare the vaccine. This concern exists for both live and killed vaccines, although, clearly, the live vaccine presents a greater problem, because the process that inactivates the virus in the killed vaccine could inactivate the contaminant as well.
4. Certain viral vaccines, namely, influenza, measles, mumps, and yellow fever vaccines, are grown in chick embryos. These vaccines should *not* be given to those who have had an **anaphylactic reaction to eggs.** People with allergies to chicken feathers can be immunized.

Inactivated (killed-virus) vaccines are made by purifying viral preparations to a certain extent and then inactivating viral infectivity in a way that does minimal damage to the viral structural proteins; mild formalin treatment is frequently used.

Killed vaccines, which are usually given intramuscularly, do not stimulate a major IgA response. Killed vaccines typically do not stimulate a cytotoxic T-cell response, because the virus in the vaccine does not replicate. Killed-virus vaccines prepared from whole virions generally stimulate the development of circulating antibody against the coat proteins of the virus, conferring some degree of resistance to that virus strain.

disadvantages of the killed vaccines
1.that they induce a **shorter duration** of protection,
2.are **less protective,**

3.and **induce fewer IgA antibodies**—
4. There is the potential problem that the inactivation process might be inadequate. Although this is rare, it happened in the early days of the manufacture of the killed polio vaccine.

However, killed vaccines do have **two advantages**:
1.they **cannot revert to virulence** and
2. They are **more heat-stable;** they therefore can be used more easily in tropical climates.

Most viral vaccines are usually given before a known exposure; i.e., they are administered **preexposure.** However, there are two vaccines, the vaccines against rabies and hepatitis B, that are also effective when given **postexposure** because the incubation period of these diseases is long enough that the vaccine-induced immunity can prevent the disease. Thus, the rabies vaccine is most often used in people after they have received a bite from a potentially rabid animal and the hepatitis B vaccine is used in people who have sustained a needle-stick injury.

The viral vaccines currently in use are described in Table –2. The vaccines, both viral and bacterial, recommended for children from 0 to 6 years of age are listed in Table –3.

Table 3– Current Viral Vaccines (2012)

Usage	**Vaccine**	**Live Virus, Killed Virus, or Subunit of Virus**
Common	Measles	Live
	Mumps	Live
	Rubella	Live
	Varicella (chickenpox)[1]	Live
	Polio	Live and killed[2]
	Influenza	Live and killed (purified subunits)[3]
	Hepatitis A	Killed
	Hepatitis B	Subunit[4]
	Rabies	Killed
	Rotavirus[5] Human papilloma virus	Live subunit
Special situations	Yellow fever[6]	Live
	Japanese encephalitis[6]	Killed

	Adenovirus	Live
	Smallpox[7]	Live

[1]There are two vaccines that contain live varicella-zoster virus: one that prevents varicella (Varivax) and another that prevents zoster (Zostavax).

[2]Only the killed vaccine is recommended for routine immunizations in the United States.

[3]The live vaccine contains a temperature-sensitive mutant of influenza virus. The killed vaccine contains two purified protein subunits (hemagglutinin and neuraminidase) obtained after the virus is chemically inactivated.

[4]Recombinant vaccine contains HBV surface antigen only.

[5]There are two live rotavirus vaccines.

[6]Used when traveling in endemic areas.

[7]Used for military personnel and certain medical personnel such as "first responders" and emergency room staff.

Table –3 Vaccines Recommended for Children Aged 0–6 Years (2012)

Bacterial Vaccines	**Viral Vaccines[1]**
Diphtheria toxoid, tetanus toxoid, acellular pertussis (DTaP)	Hepatitis A
Haemophilus influenzae type b (Hib)	Hepatitis B
Meningococcal	Influenza
Pneumococcal	Measles, mumps, rubella (MMR)
	Poliovirus, inactivated
	Rotavirus
	Varicella

[1]Human papilloma virus vaccine is recommended for females aged 9 to 26 years.

Passive Immunity

Passive immunity is provided by the administration of preformed antibody in preparations called immune globulins. The immune globulins useful in the prevention of viral diseases are

described below.

Passive–active immunity is induced by giving both immune globulins to provide immediate protection and a vaccine to provide long-term protection. This approach is described below in the sections on rabies and hepatitis B. The following preparations are available:

1. **Rabies** immune globulin (RIG) is used in the prevention of rabies in people who may have been exposed to the virus. It is administered by injecting as much RIG as possible into the tissue at the bite site and the remainder is given intramuscularly. In addition to RIG, the vaccine containing killed rabies virus should be given. RIG and the vaccine should be given at different sites. This is an example of passive–active immunization.
2. **Hepatitis B** immune globulin (HBIG) is used in the prevention of hepatitis B in people who may have been exposed to the virus either by needle-stick or as a neonate born of a mother who is a carrier of HBV. HBIG is often used in conjunction with hepatitis B vaccine, an example of passive–active immunization.
3. **Varicella-zoster** immune globulin (VZIG) is used in the prevention of disseminated zoster in people who may have been exposed to the virus and who are immunocompromised.
4. **Vaccinia** immune globulins (VIG) can be used to treat some of the complications of the smallpox vaccination.
5. Immune globulins (IGs) are useful in the prevention (or mitigation) of **hepatitis A** or **measles** in people who may have been exposed to these viruses. IGs are commonly used prior to traveling to areas of the world where hepatitis A virus is endemic.

Herd Immunity

Herd immunity (also known as community immunity) occurs when a sufficiently large percentage of the population (the "herd") is immunized so that an unimmunized individual is protected. For herd immunity to occur, the vaccine must prevent transmission of the virus as well as prevent disease. This effect is reflected in dramatic decreases in the incidence of disease, even when all susceptible individuals have not been vaccinated For example, the live, attenuated polio vaccine can provide good herd immunity because it induces intestinal IgA, which prevents poliovirus from replicating in the gastrointestinal tract and being transmitted to others. However, the killed polio vaccine does not induce herd immunity because secretory IgA is not produced and immunized individuals (although protected from poliomyelitis) can still serve as a source of poliovirus for others.

However, the threshold of immunity needed for this indirect protective effect depends on many factors, including

1. The transmissibility of the infectious agent.

2. The nature of the vaccine-induced immunity.

3. The distribution of the immune individuals.

Future Vaccine Prospects

Molecular biology and modern technologies are combining to allow novel approaches to vaccine development. Many of these approaches avoid the incorporation of viral nucleic acid in the final product, improving vaccine safety. Examples of what is ongoing in this field can be listed as follows. The ultimate success of these new approaches remains to be determined.

1. Use of recombinant DNA techniques to insert the gene coding for the protein of interest into the genome of an avirulent virus that can be administered as the vaccine (eg, vaccinia virus).

2. Including in the vaccine only those subviral components needed to stimulate protective antibody, thus minimizing the occurrence of adverse reactions to the vaccine.

3. Use of purified proteins isolated from purified virus or synthesized from cloned genes (a recombinant hepatitis B virus vaccine contains viral proteins synthesized in yeast cells). Expression of cloned gene(s) sometimes results in formation of empty virus-like particles.

4. Development of edible vaccines whereby transgenic plants synthesizing antigens from pathogenic viruses may provide new cost-effective ways of delivering vaccines.

5. Use of naked DNA vaccines—potentially simple, cheap, and safe.

6. Administration of vaccine locally to stimulate antibody at the portal of entry (eg, aerosol vaccines for respiratory disease viruses).