Vaccine Immunology — Types of Vaccines

See online here

The word vaccine, and vaccination, actually comes from the name for a poxvirus—the cowpox virus, vaccinia, to be exact. This virus was used to provide immunization against smallpox. The first use of the *term* "*vaccine*" was created by Edward Jenner in 1798.

Definition of Vaccination

A vaccine is a substance that stimulates the production of antibodies and provides immunity against 1 or several diseases, prepared from the causative agent of a disease, its products, or a synthetic substitute, treated to act as an antigen without inducing the disease. A vaccine induces protection by utilizing pre-existing components of the immune response or by inducing the generation of antigen-specific memory cells.

Both the innate and adaptive immune subsystems are necessary to provide an effective immune response to an immunization. Further, effective immunizations must induce long-term stimulation of both the humoral and cell-mediated arms of the adaptive system by the production of effector cells and memory cells.

At least 7 different types of vaccines are currently in use or in development that produces this effective immunity and have contributed greatly to the prevention of infectious disease around the world.

General requirements for a successful vaccine

- Effective
- Appropriate adaptive immune response
- Stable
- Inexpensive
- Safe

Vaccine components

Antigen: whole organism (live attenuated or killed), or subunit

Carrier: provides helper T cell epitopes, the part of an antigen molecule to which an antibody attaches

Adjuvant: non-specifically stimulates a specific immune response; depot + dendritic cell activator (= ”PAMP,” **pathogen-associated molecular patterns**, or **PAMP**s, are molecules associated with groups of pathogens, that are recognized by cells of the innate immune system called pattern recognition receptors (PRRs))

Uses of Vaccines

Prevent infection	Polio (OPV)
Control existing infection	Zoster
Prevent disease development post-exposure	Rabies
Prevent fetal infection	Rubella
Prevent or control cancer (cervical cancer, liver cancer)	Human papillomavirus (HPV)/hepatitis B virus (HBV)

Active Immunization

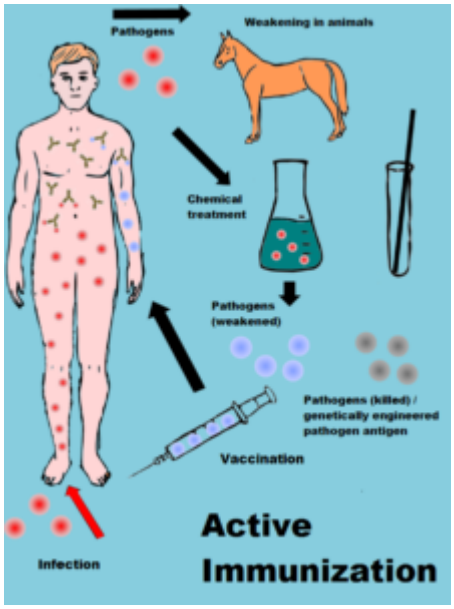


Image: “This scheme illustrates the process of active immunization and depends on the original artwork of Invexis.” by KoRe78. License: CC BY-SA 3.0

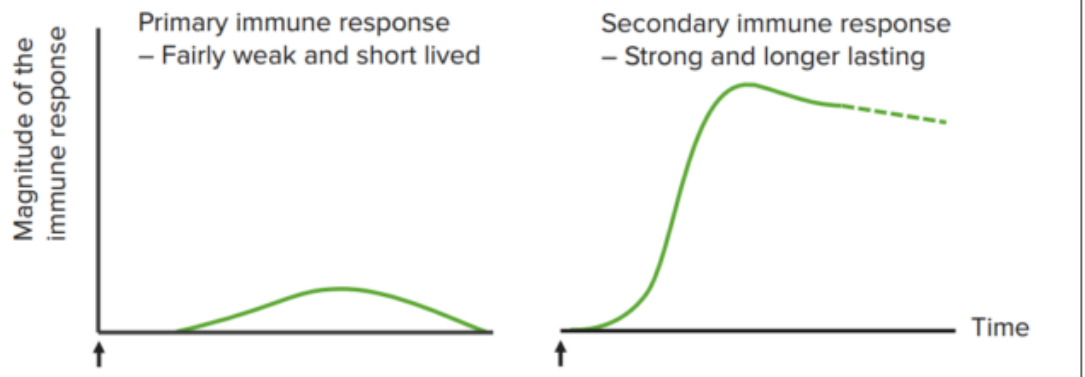
Active immunization involves the generation of acquired immunity by the application of **antigens** in the form of:

- Inactivated pathogens or their components (**dead vaccine**) or
- Pathogens attenuated in their pathogenic effects (virulence), but still proliferative (**live vaccines**)

History of active vaccination

- Ancient Chinese practice of variolation used dried smallpox scabs blown into the nose
- Produced a milder form of the disease
- 1–2% of variolated individuals die, cf. 30% who died following natural infection
- Subsequently protected from smallpox
- By 1700, variolation had been adopted in India, the Ottoman empire, and Africa
- Edward Jenner noted in England that dairymaids infected with cowpox became immune to smallpox
- In 1796 he deliberately infected a boy, James Phipps, with cowpox through scratches in the skin
- Subsequently, he exposed the boy to smallpox. The boy was protected
- Jenner published his findings in 1798, concluding that vaccination provided immunity to smallpox

Immunological basis of active vaccination



First encounter with antigens from a pathogen. Seen in a nonpathogenic form. Memory T cells and B cells are generated.	Subsequent encounter with the actual pathogen. Because memory cells are already present as a result of vaccination, a secondary immune response occurs on the 1st encounter with the pathogen.

Inactivated (Killed) Vaccines

Inactivated vaccines are weakly immunogenic, which is why **multiple applications** of the vaccine, as well as regular **booster vaccinations are** necessary after successful **basic immunization** in order to achieve adequate vaccination protection. In addition, they are low in side effects. Undesirable accompanying reactions are mainly due to the addition of adjuvants (see below).

Advantages	Disadvantages
Relatively easy to manufacture	Adjuvants required
No possibility of reversion to virulent pathogen	Typically requires initial 2–3 immunizations and then relatively frequent boosts
Safe for use in the immunocompromised	Immunity can be short-lived and predominantly humoral with poor cell-mediated immunity

Full vaccines

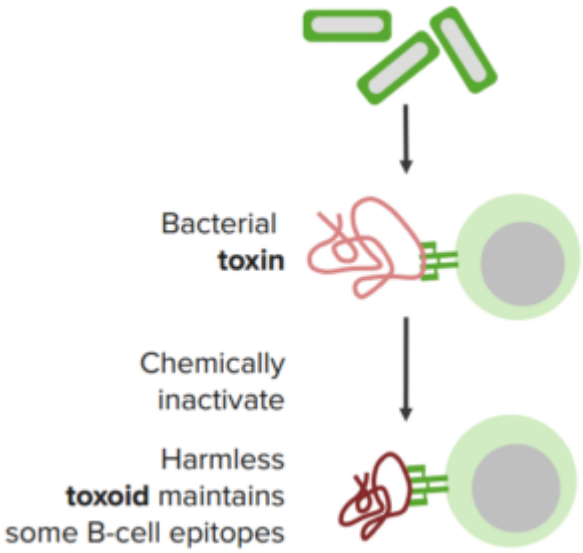
The simplest way of producing dead vaccines is the cultivation of pathogens on specific culture media (bacteria) or within cell cultures or incubated chicken eggs (viruses), followed by physicochemical purification and inactivation by heat or formaldehyde. The **full vaccines** obtained in this way have antigenic structures of the pathogen (e.g., rabies vaccine human diploid cell (HDC) and cholera).

Subunit vaccines

In contrast to full vaccines, subunit vaccines contain **pathogen antigens** which can be isolated from cultures by **purification procedures** or can be produced specifically using **recombinant DNA technology** (e.g., capsular polysaccharides of *Haemophilus influenzae* type B, *pneumococci, meningococci,* and typhoid).

Examples of subunit vaccines

Hepatitis B: recombinant hepatitis B surface antigen (HBsAg) produced in *Saccharomyces cerevisiae* HPV: recombinant L1 major capsid proteins self-assembled into virus-like particles (VLP)	
DTaP: acellular pertussis (inactivated pertussis (inactivated pertussis toxin and ≥ 1 other bacterial components e.g., filamentous hemagglutinin, pertactin [an OMP] and fimbriae, plus diphtheria toxoid, and tetanus toxoid Meningococcal serogroup B vaccines: recombinant *Neisseria meningitidis* group B proteins	



Toxoid vaccines

Purified **toxins**, which are **(formalin) inactivated** for testing purposes (toxoids), are called toxoid vaccines. Examples are the vaccines against tetanus and diphtheria.

- Chemically inactivated bacterial exotoxins
- Protect from disease but not from infection
- Examples include tetanus toxoid and diphtheria toxoid

Conjugate vaccines

Polysaccharides produce a weak immunological response based on the **T cell-independent activation of B cells**. In order to ensure lasting immunity with the formation of immunoglobulin G (IgG) and immunological memory cells, vaccines have

been developed which, **by the coupling of polysaccharides to proteins, elicit T cell-dependent B cell activation** (so-called conjugate vaccines). Conjugate vaccines are available against *pneumococci* (Prevenar®), group C *meningococci*, and *H. influenzae* type b (Hib).

- Purified bacterial capsular polysaccharides only elicit immunoglobulin M (IgM) antibodies due to lack of helper T cell epitopes
- Conjugate vaccines comprise polysaccharides coupled to protein
- Tetanus or diphtheria toxoid is often the protein of choice
- Converts T independent response to a T dependent response
- Class switching to produce high affinity IgG and immunoglobulin A (IgA) antibodies

Examples of conjugate vaccines	
Hib: *H. influenzae* type b capsular polysaccharide conjugated to tetanus toxoid	
Menigococcal conjugate vaccine: serogroups A, C, W and Y capsular polysaccharides conjugated to CRM197 (a nontoxic varaint of diphtheria toxin)	
Pneumococcal conjugate vaccine (PCV13): capsular polysaccharide antigens of 13 *Streptococcus pnuemoniae* serotypes conjugated to CRM197	

Adjuvants

Because of the low immunogenic potency of many dead vaccines (e.g., toxoid vaccines), **active enhancers** (e.g., aluminum hydroxide) are added to the purified excitatory antigens which non-specifically enhance the immune response. This is essentially achieved by a locally-induced inflammatory reaction, which leads to an increased migration of macrophages, T and B lymphocytes to the site of the pathogen application.

Example includes:

- Aluminum salts: aluminum hydroxide, aluminum phosphate, alum (potassium aluminum sulfate), or mixed aluminum salts
- AS03: oil-in-water emulsion containing D-, L-alpha-tocopherol, and squalene
- AS04: aluminum hydroxide and monophosphoryl lipid A (a low-toxicity derivative of LPS which stimulates TLR4)
- MF59: oil-in-water emulsion of squalene
- Virosomes: double membrane lecithin-phospholipid liposomes (incorporating viral proteins)

Examples of dead vaccines		
Diphtheria	Toxoid vaccine from deactivated diphtheria toxin; contains adjuvant	
Tetanus	Toxoid vaccine from deactivated tetanus toxin; contains adjuvant	
Pertussis	Acellular vaccine from different antigens	
Poliomyelitis	Salk vaccine: trivalent vaccine containing killed polioviruses from 3 different strains	
Hepatitis B	Genetically engineered vaccine containing the surface antigen (HBsAg)	
Hepatitis A	Inactivated viruses	
Haemophilus Influenzae Type b (Hib)	Conjugate vaccine containing purified capsular polysaccharides	
Pneumococcus	Conjugate vaccine containing purified capsular polysaccharides	
Meningococcus	Conjugate vaccine against serotypes A and C, which contains purified capsular polysaccharides	
Typhoid	Vaccine from purified capsular polysaccharides	
Cholera	Full vaccine from killed pathogens for intravenous administration	
FSME	Full vaccine from killed viruses	
Rabies	Full vaccine from killed viruses	
Influenza	Gap vaccines from purified antigens (hemagglutinin, neuraminidase)	

Attenuated (Live) Vaccines

Live vaccines are **attenuated** pathogens in their pathogenic effect (virulence). Most live vaccine strains have been long known. Their pathogenicity loss is due to **spontaneous mutations** which have developed under the repeated passage of animal host organisms or suitable cell lines.

Advantages	Disadvantages
Mimic natural infection thus providing appropriate responses	Slight potential to revert back to virulent form
Stimulate both humoral and cell-mediated responses	Often require refrigeration
Typically generate long-term immunity with reduced need for booster immunization	Potential for spread from vaccinee
	Contraindicated in immunocompromised due to risk of significant pathology (FREQUENT USMLE QUESTION)

Through **advances in biotechnology**, the production of genetically modified attenuated pathogens (e.g., deletion of virulence genes) is also possible more recently.

The reproducibility of the apathogenic pathogens in the vaccinated person leads to a pronounced immune reaction with the formation of **long-lasting immunity**. The prerequisite is a **functioning immune system** since the otherwise unbridled proliferation of the pathogen with the formation of possible vaccination complications can occur. **Therefore, live vaccination should not be performed on:**

- Vaccinees with defects in humoral immunity (B cell defects)
- Patients with T cell defects
- Patients under chemotherapy
- Immunocompromised patients with immunosuppressive therapy (excluding local or low-dose cortisone therapy)
- Patients after bone marrow or stem cell transplantation (at least 2 years post interventionally with sufficient immune status)

For human immunodeficiency virus (HIV) there is a vaccination recommendation for live vaccination, as long as there is no immunosuppression, measured on the cluster of differentiation 4 (CD4+) cell count (see the website of the Robert-Koch-Institute).

Examples of live vaccines		
Measles, mumps, rubella, varicella zoster virus (chickenpox/shingles) Influenza Polio (oral polio vaccine (OPV)) Rotavirus Yellow fever	Vaccines from attenuated viruses	
Oral live typhoid vaccine (Ty21a) Bacille Calmette Guérin (BCG)	Attenuated bacteria to be taken orally (typhoral)	
Cholera	Attenuated bacteria to be taken orally	

Passive Immunization

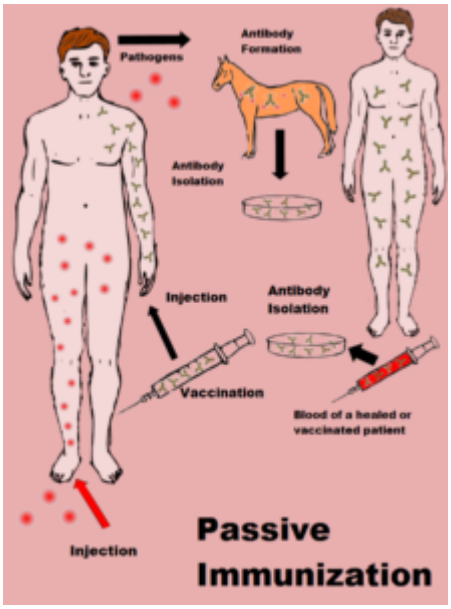


Image: “This scheme illustrates the process of passive immunization and depends on the original artwork of Invexis.” by KoRe78. License: CC BY-SA 3.0

Passive immunization involves the administration of **immunoglobulins** to rapidly build up a sufficiently high humoral immunity. Unlike in the case of active immunization, no immunological reaction and no permanent immunity are generated on the part of the vaccine. Rather, the passive immunization will serve as prophylaxis against infection after pathogen exposure (post-exposure prophylaxis (PEP)), whereby, if possible, a simultaneous vaccination with simultaneous active immunization (for example tetanus prophylaxis in unvaccinated injured persons) should be carried out.

Used antibodies are from human (**homologous antibodies**) or animal (**heterologous antibodies**) donors:

- **Homologous immunoglobulin preparations** mainly contain **IgG**. According to their production, **standard immunoglobulins** (from a pool of different donors) and hyper immunoglobulins (from the plasma of donors with high Ak titers) are distinguished. Their average half-life period is **21 days**.
- **Heterologous antibodies** consist of animal proteins and can cause **sensitization reactions**, whose frame represents the serum disease. Formation of circulating immune complexes can lead to fever, urticaria, arthritides, conjunctivitis, and proteinuria. In addition, allergic reactions up to anaphylaxis are described. For this reason, heterologous antisera should be administered exclusively intramuscularly.

Horse antisera against:

- Snake venom
- Botulism toxin
- Diphtheria toxin

Pooled human Ig against:

- Hepatitis A or B

- Measles
- Rabies
- Tetanus
- Varicella-Zoster

Humanized monoclonal against:

- Respiratory syncytial virus (RSV)

Human immunoglobulins for passive immunization		
Disease	**Immunoglobulin**	**Indication**
Measles	Human standard immunoglobulin	Immunodeficiency in children
Hepatitis A	Human standard immunoglobulin	Contact with infected person
Hepatitis B	Human hyperimmune globulin	Pathogen inoculation by needle stick injuries, if there is insufficient Hbs titer (< 10 IU/L); postnatal in newborn infants of infected mothers
Varicella-zoster	Human hyperimmune globulin	Protection of the unborn child in case of infection during pregnancy; immunocompromised persons after exposure
Rubella	Human hyperimmune globulin	Unvaccinated pregnant women who were exposed to pathogens
Rh- intolerance (anti-D-prophylaxis)	Human hyperimmune globulin	Postpartum (until 72h) with Rh-negative mother at the birth of an Rh-positive child
Tetanus	Human hyperimmune globulin	Missing/unknown vaccination protection in case of injuries along with active immunization
CMV	Human hyperimmune globulin	Immune-compromised patients
Rabies	Human hyperimmune globulin	After-bite injuries by infected animals
Diphtheria	Animal antitoxin	Especially diphtheria
Botulism	Animal antitoxin	Especially botulism

Active and Passive Immunization: Overview

Active	**Passive**
Injection of antigen	Injection of preformed antibodies
Often requires additional components — adjuvant	Protection is immediate but short term
Immune response generated *in vivo*	Only provides humoral immunity — pathogen needs to be susceptible to antibody-mediated destruction
Takes time to develop but provides long-term protection — generates memory T cells and B cells	Risk of adventitious pathogen
Potential to develop both a cell-mediated and humoral response	

Side Effects of Preventive Vaccinations

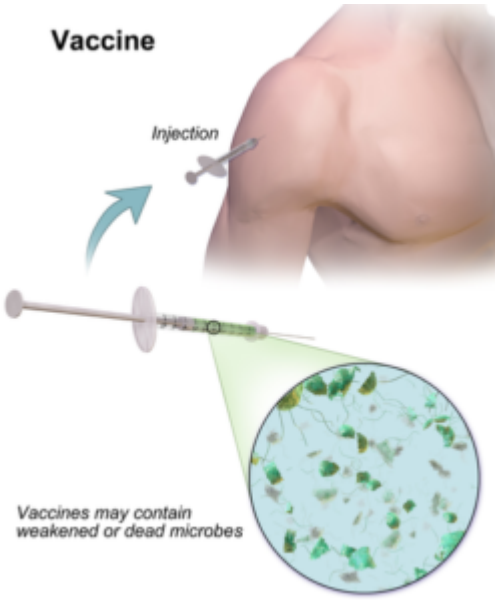


Image: “Vaccine.” by BruceBlaus. License: CC BY-SA 4.0

Regardless of the vaccine used, as a result of the immunological response of the vaccine, unpleasant but harmless vaccination reactions can occur which typically develop within the 1st 3 days after vaccination. Frequently occurring complaints are local inflammatory reactions (redness, swelling, and pain) in the area of injection. More rarely, there is a fever, muscle and joint pain, fatigue, and/or flu-like symptoms.

A **diminished form** of the disease (e.g., vaccination measles and arthralgia in rubella vaccination) is also possible in **live vaccinations**.

Vaccination complications

Vaccine complications are vaccine-specific **side effects that go beyond the normal and expected vaccination reactions**. Their probability of occurrence is very low; data are often based on individual case reports. Regarding the doctor’s duty to inform the patient, however, they are significant.

- Anaphylactic reactions (reported in various vaccines)
- Neuritis and neuropathy (diphtheria and tetanus)
- Fever cramps in infants (diphtheria, pertussis, and tetanus (DPT) combination vaccination, measles, mumps, *meningococci*, pertussis, pneumococcal conjugate vaccine, rubella)
- Guillain-Barré syndrome (FrühSommer-MeningoEnzephalitis (FSME), *H. influenzae b*, and tetanus)
- Encephalitis (tick-borne encephalitis (TBE) and measles)
- Meningitis (mumps)
- Cramps (Hep B)
- Arthritis (measles, mumps, and rubella (MMR) vaccination, rubella)

Thrombocytopenia (pneumococcal polysaccharide vaccine, measles, mumps, and rubella, and varicella (MMR-V), MMR, measles, mumps (MM), influenza, tetanus, diphtheria, and acellular pertussis (TDaP))

Egg protein allergy

By breeding various vaccines in incubated chicken eggs (measles, mumps, influenza, and yellow fever), traces of protein can be present in the vaccines. However, these are usually so marginal as a result of the purification that there is no concern about the administration in patients with a chicken protein allergy. According to the Standing Committee on Vaccination (STIKO) Recommendation (2007), **contraindication only applies to influenza and yellow fever vaccination.**

Need for New and Improved Vaccines

Annual influenza vaccine production

- Global surveillance for emerging strains
- Food and drug administration (FDA) advisory panel selects 3 strains
- Manufacture and testing
- Distribution
- Vaccination
- Time scale means insufficient vaccine to vaccinate everybody
- Ongoing research for a universal influenza vaccine

Malaria vaccine

- RTS,S/AS01 trial in Sub-Saharan Africa (2009-2011)
- A portion of circumsporozoite protein of *Plasmodium falciparum* fused to HBsAg
- Targets pre-erythrocytic stage of the parasite
- More than 15,000 infants against severe malaria in 5–17-months-old children (32.3% of children)

The BCG vaccine for tuberculosis (TB)

- BCG is an attenuated live Bacille Calmette Guérin strain of *Mycobacterium bovis*
- Used in countries with high prevalence of TB to prevent childhood tuberculosis, meningitis, and miliary disease
- Not generally recommended in the United States due to low risk of infection with *Mycobacterium tuberculosis*, variable effectiveness against adult pulmonary TB, and potential interference with tuberculin skin test

Considered only for:

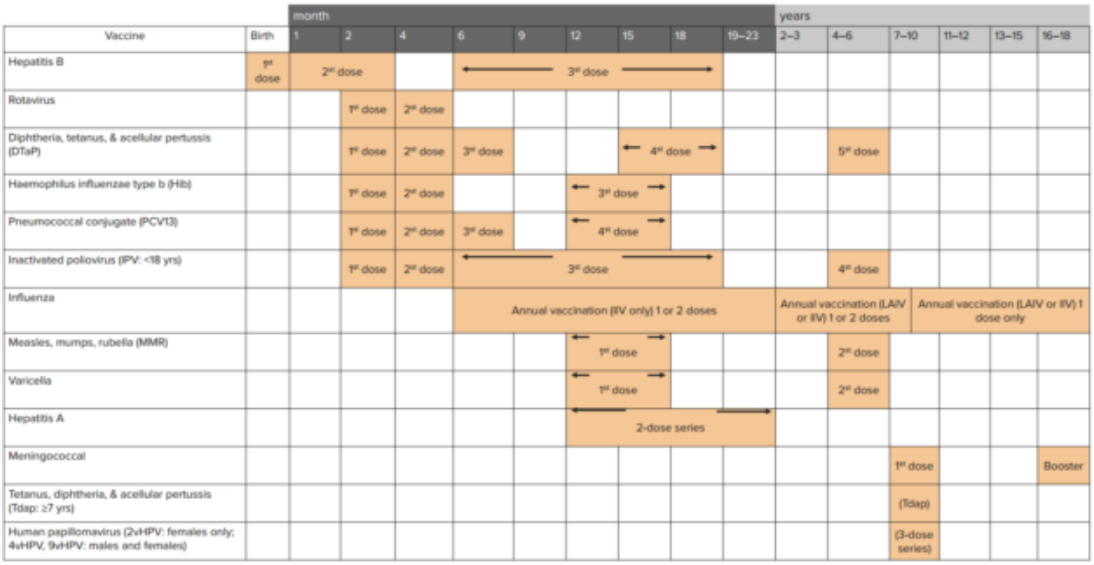
- Children who have a negative tuberculin skin test and at high risk, e.g., continually exposed to isoniazid and rifampin-resistant *M. tuberculosis*
- Health care workers routinely exposed to drug-resistant *M. tuberculosis*

HIV vaccines

- Success requires identification of immunogens and immunization strategy that induces broad and long-lasting cytotoxic T cell lymphocyte (CTL) immunity together with broadly neutralizing antibodies
- Broadly neutralizing antibodies identified in very small number of people living

with HIV and intravenous infusion of such antibodies is entering clinical trials
- No vaccine tested in clinical trials so far has been sufficiently successful
- Thailand trial in 2009: 4 priming injections of recombinant canarypox vector containing HIV gag, polymerase (pol) and envelope (env) genes, 2 booster injections with recombinant gp120; limited protective effect with an efficacy of 25–30%
- Current South Africa trial using a similar vaccine

Childhood vaccination schedule in USA (2016)



Future needs for vaccination

- Eradication of polio
- Effective vaccines for HIV, TB, and malaria
- Broadly-specific influenza vaccine
- Therapeutic vaccines — hepatitis, HIV, and cancer
- Vaccines against parasites

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Notes