Autumn time is flu time! A reason for many medical doctors to get vaccinated and to take the opportunity to take a look at their vaccination certificate. But what else do you know about tetanus, diphtheria, and co? And how are the different vaccines different in their nature and preparation?

The word vaccine, and vaccination, actually comes from the name for a pox virus—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 one or several diseases, prepared from the causative agent of a disease, its products, or a synthetic substitute, treated to act as an antigen without
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 seven different types of vaccines are currently in use or in development that produce 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 PAMPs, 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

<table>
<thead>
<tr>
<th>Prevent infection</th>
<th>Polio (OPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control existing infection</td>
<td>Zoster</td>
</tr>
<tr>
<td>Prevent disease development post-exposure</td>
<td>Rabies</td>
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</table>
Active Immunization

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 dies, 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 first 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).

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

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 all antigenic structures of the pathogen (e.g. rabies vaccine HDC, 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, typhoid).

Examples of subunit vaccines
Hepatitis B: recombinant hepatitis B surface antigen (HBsAg) produced in *Saccharomyces cerevisiae*. Human papillomavirus (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 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 Haemophilus influenzae type b (Hib).

- Purified bacterial capsular polysaccharides only elicit 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 IgA antibodies

### Examples of conjugate vaccines

<table>
<thead>
<tr>
<th>Hib: <em>Haemophilus influenzae</em> type b capsular polysaccharide conjugated to tetanus toxoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menigococcal conjugate vaccine: serogroups A, C, W and Y capsular polysaccharides conjugated to CRM197 (a nontoxic variant of diphtheria toxin)</td>
</tr>
<tr>
<td>Pneumococcal conjugate vaccine (PCV13): capsular polysaccharide antigens of 13 Streptococcus pneumoniae serotypes conjugated to CRM197</td>
</tr>
</tbody>
</table>

### 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

- Diptheria: toxoid vaccine from deactivated diptheria 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
- FSM: 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.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mimic natural infection thus providing appropriate responses</td>
<td>Slight potential to revert back to virulent form</td>
</tr>
<tr>
<td>Stimulate both humoral and cell-mediated responses</td>
<td>Often require refrigeration</td>
</tr>
<tr>
<td>Typically generate long-term immunity with reduced need for booster immunization</td>
<td>Potential for spread from vaccinee</td>
</tr>
</tbody>
</table>

**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 a **long-lasting immunity**. The prerequisite is a **functioning immune system** since 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 HIV there is a vaccination recommendation for live vaccination, as long as there is no immunosuppression, measured on the CD4 + cell count (see the website of the Robert-Koch-Institute).

<table>
<thead>
<tr>
<th>Examples of live vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles, mumps, rubella, varicella zoster virus (chickenpox/shingles), influenza, Polio (OPV), Rotavirus, Yellow Fever</td>
</tr>
<tr>
<td>Oral live typhoid vaccine (Ty21a), Bacille Calmette Guérin (BCG)</td>
</tr>
<tr>
<td>Cholera</td>
</tr>
</tbody>
</table>
Passive Immunization

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 a prophylaxis against an infection after pathogen exposure (postexposure 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 *hyperimmunoglobulins* (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)

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

Active and Passive Immunization: Overview

<table>
<thead>
<tr>
<th>Active</th>
<th>Passive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection of antigen</td>
<td>Injection of pre-formed antibodies</td>
</tr>
<tr>
<td>Often requires additional components — adjuvant</td>
<td>Protection is immediate but short term</td>
</tr>
<tr>
<td>Immune response generated <em>in vivo</em></td>
<td>Oly provides humoral immunity — pathogen needs to be susceptible to antibody-mediated destruction</td>
</tr>
<tr>
<td>Takes time to develop but provides long-term protection — generates memory T-cell and B-cells</td>
<td>Risk of adventitious pathogen transfer</td>
</tr>
<tr>
<td>Potential to develop both a cell-mediated and humoral response</td>
<td></td>
</tr>
</tbody>
</table>
Side Effects of Preventive Vaccinations

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 first three days after vaccination. Frequently occurring complaints are **local inflammatory reactions (redness, swelling, 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, 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, neuropathy (diphtheria, tetanus)
- Fever cramps in infants (DPT combination vaccination, measles, mumps, meningococci, pertussis, pneumococcal conjugate vaccine, rubella)
- **Guillain-Barré syndrome** (FSME, Haemophilus influenzae b, tetanus)
- Encephalitis (TBE, measles)
- Meningitis (mumps)
- Cramps (Hep B)
- **Arthritis** (MMR vaccination, rubella)
- **Thrombocytopenia** (pneumococcal polysaccharide vaccine, MMR-V, MMR, MM, influenza, TDaP)
Egg protein allergy

By breeding various vaccines in incubated chicken eggs (measles, mumps, influenza, 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 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
- 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)
- Portion of circumsporozoite protein of *Plasmodium falciparum* fused to hepatitis B surface antigen
- Targets pre-erythrocytic stage of the parasite
- > 15,000 infants against severe malaria in 5—17 months old children of 32.3%

The BCG vaccine for tuberculosis (TB)

- BCG is an attenuated live Bacille Calmette Guerin strain of *Mycobacterium bovis*
- Used in countries with high prevalence of TB to prevent childhood tuberculosis, meningitis and miliary disease
- Not generally recommended in USA 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 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, pol & env genes, 2 booster injections with recombinant gp120; limited protective effect with efficacy of 25—30%
- Current South Africa trial using similar vaccine

Childhood vaccination schedule in USA (2016)

Future needs for vaccination

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

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