Vaccine and Vaccination

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Vaccine Term

The term vaccination
Latin word *vacca*, means a cow
The first inoculations were given with organisms that caused the mild disease cowpox to produce immunity against smallpox
Vaccination

**Vaccination** is the use of vaccines to prevent specific diseases.

**Vaccination (Immunization)**
Inoculation of a host with inactive or weakened pathogens or pathogen products to stimulate protective immunity.

**Vaccine**
An inactivated or weakened pathogen, or an innocuous pathogen product used to stimulate protective immunity.
Vaccination is referred to the process of stimulating protective immune responses in animals against pathogenic microorganisms by exposing them to non-pathogenic forms or components of the microorganisms.

A successful vaccine induces an effective adaptive immune response directed at appropriate target antigens on the pathogen without causing disease in the recipient.

The types of vaccines are those composed of inactivated microorganisms, live attenuated microorganisms, microbial products, synthetic peptides and DNA of microbial origin.
• **Bacteremia**: The presence of microorganisms in the blood.

• **A bacterin** is a vaccine comprised of killed bacterial cells in suspension. Inactivation is by either chemical or physical treatment.

• **A live vaccine** is an immunogen for protective immunization that contains an attenuated strain of the causative agent.

• **A challenge** is the deliberate administration of an antigen to induce an immune reaction in an individual previously exposed to that antigen to determine the state of immunity.

• **Toxicity**: the pathogenicity caused by toxins produce by a pathogen.
• **Vaccinable** is the capability of being vaccinated successfully.

• **A mixed vaccine** is a preparation intended for protective immunization that contains antigens of more than one.

• **Formol toxoid** is a toxoid generated by the treatment of an exotoxin such as diphtheria toxin with formalin.

• **Anavenom** is a toxoid consisting of formalin-treated snake venom which destroys the toxicity but preserves immunogenicity of the preparation.
• **An inactivated vaccine** is an immunizing preparation that contains microorganisms such as bacteria or viruses that have been killed to stop their replication while preserving their protection-inducing antigens.

• **Immunoprophylaxis** describes disease prevention through the use of vaccines to induce active immunization or antisera to induce passive immunization.

• **An autogenous vaccine** is prepared by isolating and culturing of microorganisms from an infected subject.
• **A lapinized vaccine** is a preparation used for immunization that has been attenuated by passage through rabbits until its original virulence has been lost.

• **LEP (low egg passage)** is a type of vaccine for rabies that has been employed for the immunization of dogs and cats.

• **HEP** is the abbreviation for “high egg passage,” which signifies multiple passages of rabies virus through eggs to achieve attenuation for preparation of a vaccine appropriate for use in immunizing cattle.

• **A polyvalent vaccine** is comprised of multiple antigens from more than one strain of a pathogenic microorganism or from a mixture of immunogens such as the diphtheria, pertussis, and tetanus toxoid preparation.
• A **caprinized vaccine** is a preparation used for therapeutic immunization, which contains microorganisms attenuated by passage through goats.

• An **edible vaccine** is a genetically altered food containing microorganisms or related antigens that may induce active immunity against infection.

• A **homologous vaccine** is an autogenous vaccine.

• **Conjugate vaccine** is an immunogen comprised of polysaccharide bound covalently to proteins.
A killed vaccine is an immunizing preparation comprised of microorganisms, either bacterial or viral, that are dead but retain their antigenicity.

- **Canine parvovirus vaccine**: Initially, a feline enteritis vaccine that was live and attenuated was used based on its cross-reactivity with canine parvovirus.

- **Newcastle disease vaccines include**: (1) an inactivated virus raised in chick embryos that is incorporated into aluminum hydroxide gel adjuvant, and (2) live virus grown in chick embryos and attenuated in a graded manner.

- **An idiotype vaccine** is an antibody preparation that mimics antigens at the molecular level.
• **A recombinant vaccine** is an immunogen preparation for prophylactic immunization, comprised of products of recombinant DNA methodology, prepared by synthesizing proteins employing cloned complementary DNA.

• **A reassortant vaccine** is an immunizing preparation in which antigens from several viruses or from several strains of the same virus are combined.

• **Prophylactic immunization** is a procedure to prevent disease through either active immunization or passive immunization.
Immunity
Adequate for the prevention of infectious diseases.

Immunization
• Passive Immunization
• Acquire Immunization (Vaccination).

Passive Immunization:
It is carried out by injection of suitable immunoglobulin.

Types of antimicrobial Vaccines
• Purified Immunogens
• Whole Killed Organisms
• Live Attenuated Organisms
Vaccines currently in use or being developed
The antibody responses of a randomly selected population of vaccinated healthy animals follow a normal distribution.
The duration of protection following vaccination is influenced by many host factors including:

- Age
- Immune competence
- The presence of maternal antibodies in the animal’s circulation.

Vaccines can contribute to the improvement of welfare problems in domestic animals, to improvement in productivity and to reduction in the need for chemotherapeutic intervention.
Vaccination has defined limitations in common with many disease control measures.

Effective vaccines for controlling equine infectious anaemia and African swine fever are not available at present.

Protective immunity against *Staphylococcus aureus* using vaccination cannot be induced in a predictable manner and prevention of fungal infections through vaccination has had limited success.
The addition of appropriate adjuvants to vaccines:

1. Enhance

2. Prolong the duration of the immune response.
Live attenuated vaccines can produce adverse reactions including immunosuppression.

Inactivated vaccines Infectious agents can be killed without substantially altering the immunogenicity of their antigens which induce protective immunity.

Most inactivating chemicals do alter the immunogenicity of infectious agents, some, such as formaldehyde, cause limited antigenic change.
In preparing inactivated vaccines, it should be taken safety measures to ensure complete inactivation of the infectious agents as the chemicals used can cause aggregation of particles thereby allowing survival of some microorganisms in the center of aggregated material.
Chemicals used for the preparation of inactivated bacterial and viral vaccines include

Formaldehyde

β-propiolactone

Ethyleneimine
Inactivated viral or bacterial preparations can be partially purified and combined with adjuvants to enhance their immunogenicity.

Inactivated vaccines have a greater antigenic mass and more frequent administration of vaccine (booster injections) are required to achieve results comparable to those obtained with live attenuated vaccines.
Live attenuated vaccines apart from the orf (contagious pustular dermatitis or contagious ecthyma) vaccine which is used in sheep, few virulent living organisms are used as vaccines in animals.

The bacillus of Calmette-Guerin, a strain of *Mycobacterium bovis*, was attenuated by culture in a bile-supplemented medium over many years.
Viruses can be attenuated by growing them in monolayers cells prepared from species to which they are not naturally adapted.

Chick embryo attenuation has been employed successfully for rabies virus.
- Prolonged culture of canine distemper virus in canine kidney cells produced strains of reduced virulence suitable for immunization of dogs.

- Measles virus has been used to vaccinate dogs against distemper and, although these viruses cross-react, maternal antibodies to distemper virus in pups do not neutralize the live measles vaccine virus.

- The use of turkey herpesvirus to control Marek’s disease in chickens is another example of protection induced by an antigenically related virus.
Live attenuated vaccines have many potential advantages over inactivated vaccines.

- They can be administered by a number of routes and present all the relevant antigens required for the induction of protective immunity since they multiply in the recipient.

- They usually induce a satisfactory level of cell-mediated and humoral immunity at sites where protection is required such as mucosal surfaces.

- Because they replicate in the body, adjuvants are not required.

- Booster doses, if required, can be given at widely spaced intervals as these vaccines induce a good immunological memory.
Disadvantages of these modified live vaccines include:

1. Immunosuppressive effects, especially in young animals or where an immunodeficient state exists.

2. While live attenuated vaccines have been used for decades, the exact nature of the changes responsible for attenuation is often unknown.

3. The circumstances in which reversion to virulence might occur cannot be predicted in a reliable manner.

4. Live attenuated viral vaccines can be contaminated with infectious agents which can induce disease in recipients.
Because maternal antibodies, acquired through ingestion of colostrum, can neutralize live viral vaccines, administration of such vaccines to young animals should be deferred until maternal antibodies have declined to low levels.

The use of particular live viral vaccines in pregnant animals is contraindicated because of the risk of congenital defects in the developing foetus.

A live viral vaccine has a limited shelf-life and should be refrigerated during transportation and storage to ensure its viability.
Vaccines produced by recombinant nucleic acid technology

Recombinant vaccines are classified into three categories:

**Type I vaccines** are composed of antigens produced by recombinant nucleic acid technology or genetic engineering.

**Type II vaccines** consist of genetically attenuated microorganisms.

**Type III vaccines** are composed of modified live viruses or bacteria into which DNA encoding protective antigens are introduced by cloning.
Type I vaccines are composed of subunit proteins produced by recombinant bacteria or other microorganisms.

- DNA encoding the required antigen is cloned in a suitable bacterium or yeast strain in which the recombinant antigen is expressed.

- These vaccines usually contain adjuvants which are required to enhance the immunogenicity of the purified antigen derived from the recombinant microorganism.

- Type I vaccines have been developed for a number of bacterial and viral pathogens. They have been used against the virus of foot-and-mouth disease, feline leukaemia virus, and *Borrelia burgdorferi*, the cause of Lyme disease.
Type II recombinant vaccines consist of virulent microorganisms that are rendered less virulent by gene deletion/knock-out or site-directed mutagenesis.

- The genome of large DNA viruses, such as herpes viruses, contains many non-essential genes.

- Using genetic engineering techniques, an Aujeszky’s disease vaccine in which an attenuated virus lacking the gene encoding thymidine kinase (TK) was developed.

- As TK is normally required by wild-type herpes viruses to replicate in non-dividing cells such as neurons, TK-attenuated herpes viruses can infect neurons but are unable to replicate in these cells.
Similar strategies have also been used to provide vaccines targeting pathogenic bacteria of veterinary importance.

In these bacteria, genes essential for key metabolic processes are often targeted for modification.

As an example, a live recombinant bacterial vaccine prepared from *Streptococcus equi* TW928 was designed, in which a 32-bp deletion in the *aroA*-encoding gene.

Submucosal administration of this knock-out vaccine confers protection in horses.
Type III vaccines are composed of modified live organisms called vectors into which a gene encoding an antigenic determinant is introduced.

In order to produce safe viral vaccine vectors it is necessary to ensure that the vector itself does not pose a threat to vaccinated animals or humans.

This can be achieved by attenuating the viral vector or by generating live attenuated viruses with precise genetic alterations that ensure their suitability as vectors.
Recombinant nucleic acid technology provides a more complete understanding of the genetic organization of viruses, permitting the identification of suitable regions for insertion of foreign DNA.

Several types of potentially useful viral vectors from a variety of viruses such as pox viruses (including vaccinia virus and fowl pox virus), adenoviruses, herpes viruses and retro-viruses, have been developed.

Potential advantages of the use of viral vectors for vaccine delivery include possible administration to large groups of animals by aerosols or in water rather than by injection of individual animals.
Such mass administration procedures would be particularly relevant to poultry and pig producers.

If properly designed, the vector should express those antigens from the pathogen that are required to induce a protective immune response thereby reducing or eliminating the chance of disease in animals exposed to the infectious agent in a modified live form.

A distinct advantage of vectored vaccines is that they can induce both humoral and cell-mediated immune responses, including strong cytotoxic T cell immunity.
In addition, some vectored vaccines may be capable of inducing local immune responses on mucosal surfaces.

To ensure vector stability and the appropriate expression of foreign DNA, only a limited amount of that genetic material can be incorporated into the vector genome.

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To ensure vector stability and the appropriate expression of foreign DNA, only a limited amount of that genetic material can be incorporated into the vector genome.

Consequently, each vectored vaccine can produce only one or a relatively small number of foreign antigens in the host animal for the induction of a protective immune response.
Currently a small number of viral vectored vaccines have been approved for use in animals.

A vaccinia vaccine vector carrying the rabies G glycoprotein has been used successfully as an oral vaccine administered to wild carnivores in bait.

The G glycoprotein induces virus-neutralizing antibodies in vaccinated animals which protect against rabies.

Other examples include a canary pox virus-vectored vaccine against canine distemper virus in dogs, West Nile virus in horses and a fowlpox virus-vectored vaccine designed to protect against avian influenza virus in poultry.
<table>
<thead>
<tr>
<th>Microbial pathogen</th>
<th>Species affected</th>
<th>Associated disease</th>
<th>Vaccine characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Brucella abortus</em></td>
<td>Cattle</td>
<td>Brucellosis</td>
<td>Spontaneous rifampicin-resistant rough mutant</td>
</tr>
<tr>
<td>Canine distemper virus</td>
<td>Dogs</td>
<td>Distemper</td>
<td>Canary pox virus-vectored vaccine</td>
</tr>
<tr>
<td>Porcine herpesvirus 1</td>
<td>Pigs</td>
<td>Aujeszky’s disease</td>
<td>Thymidine kinase-deleted marker vaccine</td>
</tr>
<tr>
<td>Porcine circovirus 2</td>
<td>Pigs</td>
<td>Post-weaning multisystemic wasting syndrome</td>
<td>Inactivated baculovirus expressing porcine circovirus 2 ORF2 protein, with adjuvant</td>
</tr>
<tr>
<td><em>Streptococcus equi</em></td>
<td>Horses</td>
<td>Strangles</td>
<td>Live vaccine administered submucosally: ΔaroA</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Horses</td>
<td>West Nile virus infection</td>
<td>DNA vaccine</td>
</tr>
</tbody>
</table>
Synthetic peptide vaccines If the structure of epitopes that can induce a protective immune response is known, it is possible to chemically synthesize peptides corresponding to these antigenic determinants.

Only a small portion of antigenic molecules interact with specific receptors on B cells and T cells.

For B cells, an antibody interacts with up to five amino acids in its antigen-binding site.

Epitopes for T cell receptors can be composed of 12 to 15 amino acids.
The general approach with synthetic peptide vaccines is to identify potential epitopes in the protein antigen and to synthesize a series of peptides corresponding to that amino acid sequence.

The immunological activity of these molecules is then evaluated *in vivo*.

This approach is appropriate only for epitopes consisting of contiguous amino acids referred to as linear epitopes.

The majority of natural epitopes are non-linear and are, therefore, dependent on the conserved three-dimensional structure of the molecule.
Antibodies induced by peptide vaccines may not react with the native molecule and, in addition, peptides are usually poor immunogens due to their small size.

Immunogenicity can be enhanced with appropriate carrier molecules or adjuvants.

Limited progress has been made with synthetic peptides for the induction of protective immune responses against infectious agents.
DNA vaccines one of the most significant developments in vaccine production in recent years involves the use of DNA, encoding microbial antigens cloned in a bacterial plasmid, for immunization.

The procedure involves injection of a plasmid containing the DNA sequence for a protective antigen whose expression is controlled by a strong mammalian promoter.

For an infectious agent expressing that antigen, injection of this recombinant plasmid into the skin or muscle of animals may result in the production of the protein inducing immunity against that infectious agent.
This leads to the expression in host cells of the encoded genes with the development of a significant immune response to the gene product in the recipient.

Unlike viral vectors, the recombinant plasmid cannot replicate in the mammalian cells but transfected host cells express the vaccine antigen.

Methods of delivery include direct intramuscular injection and the use of liposomes or coated gold particles fired by a gene gun.

Although transfection rates appear low, antigen production has been detected in animals vaccinated with DNA intramuscularly for up to 6 months after injection.
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Because DNA vaccination induces intracellular processing of antigen, it seems to mimic a natural infection and is, therefore, an effective method of inducing T cell responses.

Even small amounts of DNA can stimulate strong cell-mediated responses.
Humoral responses, however, may not be as high as those obtained by injection of a purified antigen.

A strategy in which priming with DNA vaccines is followed by boosting with attenuated viral vectors such as fowl poxvirus and modified vaccinia virus has produced exceptionally strong immune responses.

The success of consecutive administration of DNA vaccines and attenuated viral vectors was attributed to the ability of the DNA vaccines to generate T cells of high affinity which were further stimulated by boosting with non-replicating viral vectors.
The following slide is an example of peptides or virus particles used in vaccination.

*In vitro* cloning of a population of bluetongue virus particles using reverse genetics for subsequent *in vivo* assessment of their suitability for vaccine production.

Bluetongue virus (BTV) is a member of the *Reoviridae* family with a genome consisting of 10 double-stranded RNA segments, each consisting of a unique ORF.

A complementary DNA (cDNA) copy of each ORF is cloned into a T7 plasmid, between a flanking upstream strong T7 promoter and a downstream restriction site.
Isolation and purification of the double-stranded RNA of bluetongue virus (BTV)

Cloning of the 10 individual double-stranded RNA segments

Expression of individual gene segments using T7 RNA polymerase

Determination of the molecular weight of each genome segment by agarose gel electrophoresis

Co-transfection of a susceptible cell line in vitro using the cloned double-stranded RNA

Selection of plaques containing cloned BTV followed by amplification in tissue culture
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommendation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBR (Infectious Bovine Rhinotracheitis)</td>
<td>Recommended</td>
<td>Annual (killed or intranasal)</td>
</tr>
<tr>
<td>BVD (Bovine Virus Diarrhea)</td>
<td>Recommended</td>
<td>Annual</td>
</tr>
<tr>
<td>PI3 (Parainfluenza virus)</td>
<td>Recommended</td>
<td>Annual</td>
</tr>
<tr>
<td>BRSV (Bovine Respiratory Syncytial Virus)</td>
<td>Recommended</td>
<td>Annual</td>
</tr>
<tr>
<td>Condition</td>
<td>Frequency</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Leptospirosis (5-Way)</td>
<td>Recommended</td>
<td>Annual (every 3 to 6 months in some areas)</td>
</tr>
<tr>
<td>Vibriosis</td>
<td>Recommended</td>
<td>Annual (30 to 60 days before breeding)</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>Optional</td>
<td>Annual (30 to 60 days before breeding)</td>
</tr>
<tr>
<td>Pinkeye</td>
<td>Optional</td>
<td>As needed</td>
</tr>
<tr>
<td>Blackleg 7-Way</td>
<td>Optional</td>
<td>Annual</td>
</tr>
<tr>
<td>Anthrax</td>
<td>Optional</td>
<td>As directed</td>
</tr>
</tbody>
</table>
Lambs and Kids:

Vaccinate for **C, D and T** (*Clostridium perfringens* type C & D plus tetanus) by 8 weeks of age, with a booster dose 4 weeks later.

If blackleg is prevalent in your area, **Covexin 8** can be used instead, to protect against blackleg as well as overeating disease and tetanus.
Lambs and Kids:

Vaccinate for pasteurella caused by *Mannheimia haemolytica* at 8-12 weeks of age, with a booster at 12-16 weeks of age.

Elective vaccines to consider based on risk of exposure include those protecting against Caseous lymphadenitis, Foot rot and Sore mouth.
Ewes, Rams:

If previously vaccinated, booster with one dose annually, preferably 2-4 weeks prior to giving birth so that protection is passed through the colostrum to the newborns.

In addition, breeding stock may be vaccinated for reproductive diseases caused by Chlamydia and Campylobacter.
<table>
<thead>
<tr>
<th>Passive</th>
<th>Active</th>
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</thead>
<tbody>
<tr>
<td><strong>Disease</strong></td>
<td><strong>Vaccine</strong></td>
</tr>
<tr>
<td>Hepatitis A, B</td>
<td>Measles</td>
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<tr>
<td></td>
<td>Measles</td>
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<tr>
<td></td>
<td>Mumps</td>
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<td></td>
<td>Yellow fever</td>
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<td>Smallpox</td>
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<td>Rubella</td>
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<td>Polio</td>
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<td></td>
<td>influenza</td>
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<tr>
<td></td>
<td>Rabies</td>
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<tr>
<td></td>
<td>Hepatitis B</td>
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<tr>
<td>CMV (Cytomegalovirus)</td>
<td>Viral</td>
</tr>
<tr>
<td>Rabies</td>
<td>Live</td>
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<td></td>
<td>Live (Sabin)</td>
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<td></td>
<td>Killed</td>
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<td></td>
<td>Killed</td>
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<tr>
<td></td>
<td>Recombinant (killed)</td>
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<tr>
<td>Gas Gangrene</td>
<td>Tetanus</td>
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<tr>
<td>Tetanus</td>
<td>Toxoid</td>
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<td>toxoid</td>
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<tr>
<td></td>
<td>Killed</td>
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<tr>
<td></td>
<td>Killed, 2 serotypes</td>
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<td></td>
<td>Killed</td>
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<td>Killed, 23 polysaccharides</td>
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<td>Killed</td>
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<td>Killed</td>
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<td>Live (BCG)</td>
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</tbody>
</table>
Vaccination Failure

Animal-related factors
- Infection (incubating the disease)
- Immunosuppression caused by drugs or infectious agents
- Genetic influences on immune responsiveness
- Passive protection by colostral antibodies (neutralization of live viral vaccines)
- Immunodeficient state due to developmental defects or the deleterious effects of infectious agents or toxic factors
- Exposed to a heavy challenge dose of infectious agent shortly after vaccination

Vaccine-related factors

Characteristics of vaccine
- Out-of-date
- Stored at incorrect temperature, loss of potency
- Exposed to sunlight with resultant partial inactivation
- Ineffective vaccine, incapable of inducing protective immunity
- Wrong strain or serotype of pathogen
- Death of live vaccine

Vaccine reconstitution and administration
- Lyophilized vaccine reconstituted with inappropriate diluent
- Incorrect route of administration
- Aerosolized vaccine not distributed properly among animals
- Contamination of multidose containers by the use of non-sterile equipment
Categories of **adjuvants** in current use or currently being evaluated.

<table>
<thead>
<tr>
<th>Category/examples</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial derivatives</strong></td>
<td></td>
</tr>
<tr>
<td>Muramyl dipeptides</td>
<td>Adjuvant activity attributed to stimulation of macrophages, dendritic cells, interferon-γ production and TH cell activation</td>
</tr>
<tr>
<td>Monophosphoryl lipid A</td>
<td>Enhanced migration of dendritic cells, generation of TH1 responses, production of IL-2, IL-12 and interferon-γ</td>
</tr>
<tr>
<td>Lipid A derivatives</td>
<td></td>
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<tr>
<td>Heat-labile enterotoxins of <em>E. coli</em></td>
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<td>Adjuvant activity attributed to stimulation of macrophages, dendritic cells, interferon-γ production and T&lt;sub&gt;H&lt;/sub&gt; cell activation</td>
</tr>
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<td>Monophosphoryl lipid A</td>
<td>Enhanced migration of dendritic cells, generation of T&lt;sub&gt;H1&lt;/sub&gt; responses, production of IL-2, IL-12 and interferon-γ</td>
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<tr>
<td><strong>examples</strong></td>
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<tr>
<td>Trehalose dimycolate</td>
<td></td>
</tr>
<tr>
<td><strong>Cytokines and related substances</strong></td>
<td></td>
</tr>
<tr>
<td>IL-1, IL-2, IL-12, Interferon-γ</td>
<td>Effective adjuvants if combined with antigenic material; can be used to direct the immune response in a given direction</td>
</tr>
<tr>
<td>C3d</td>
<td></td>
</tr>
<tr>
<td><strong>Emulsions</strong></td>
<td></td>
</tr>
<tr>
<td>Water-in-oil emulsions</td>
<td>These oil-based preparations are considered depot adjuvants; inclusion of heat-killed mycobacteria enhances immune responses; they stimulate antigen-presenting cells, T and B lymphocytes</td>
</tr>
<tr>
<td>Mineral oil</td>
<td></td>
</tr>
<tr>
<td>Vegetable oil</td>
<td></td>
</tr>
<tr>
<td>Montanide ISA</td>
<td></td>
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<tr>
<td>Squalene</td>
<td></td>
</tr>
<tr>
<td>Oil-in-water emulsion MF 59 (squalene with Tween 80 and Span 85)</td>
<td>Seems to act through localization of injected material in antigen-presenting cells; promotes TH2 cell development and production of IgG antibody</td>
</tr>
<tr>
<td><strong>Biodegradable particles</strong></td>
<td></td>
</tr>
<tr>
<td>Liposomes</td>
<td>Taken up by antigen-presenting cells and processed by MHC class II-dependent pathways</td>
</tr>
<tr>
<td>Virosomes</td>
<td>Fuse with cell membranes, enclosed antigen presented via MHC class I-dependent pathways, effective cytotoxic T lymphocyte responses reported</td>
</tr>
<tr>
<td>Proteosomes</td>
<td>Taken up by antigen-presenting cells; promote TH1 responses</td>
</tr>
<tr>
<td>Virus-like particles</td>
<td>Immunogenicity strong without additional adjuvant</td>
</tr>
<tr>
<td>Category/examples</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Aluminium hydroxide, aluminium phosphate, calcium phosphate, aluminium potassium sulphate</td>
<td>Adjuvant activity related to macrophage activation and increased uptake of antigen by antigen-presenting cells; promote $T_H2$ cell responses and enhance antibody production</td>
</tr>
<tr>
<td>Saponins</td>
<td>Saponin-based adjuvants augment $T_H1$ and $T_H2$ cell responses; ISCOM-based vaccines promote both humoral and cell-mediated immune responses; activity of ISCOMs attributed to interactions with macrophages and dendritic cells and activation of $CD4^+T$ cells</td>
</tr>
<tr>
<td>Immunostimulating complexes (ISCOMs)</td>
<td></td>
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- Infection (incubating the disease)
- Immunosuppression caused by drugs or infectious agents
- Genetic influences on immune responsiveness
- Passive protection by colostral antibodies (neutralization of live viral vaccines)
- Immunodeficient state due to developmental defects or the deleterious effects of infectious agents or toxic factors
- Exposed to a heavy challenge dose of infectious agent shortly after vaccination

Vaccine-related factors
- Characteristics of vaccine
  - Out-of-date
  - Stored at incorrect temperature, loss of potency
  - Exposed to sunlight with resultant partial inactivation
  - Ineffective vaccine, incapable of inducing protective immunity
  - Wrong strain or serotype of pathogen
  - Death of live vaccine
- Vaccine reconstitution and administration
  - Lyophilized vaccine reconstituted with inappropriate diluent
  - Incorrect route of administration
  - Aerosolized vaccine not distributed properly among animals
  - Contamination of multidose containers by the use of non-sterile equipment
BOX 5.2 Potential adverse reactions following vaccination.

- Local or systemic infection caused by contamination of live vaccine with extraneous agents
- Disease produced by the survival of infectious agents in a supposedly killed vaccine
- Disease produced by resistant infectious agents such as prions surviving in inactivated vaccines
- Disease production by live vaccine in immunosuppressed animals
- There may be a risk of congenital defects if particular live vaccines are administered to pregnant animals
- Vaccine-induced immunosuppression
- Development of hypersensitivity reactions to vaccine components (immediate or delayed responses)
- Adjuvants containing mineral oil may induce a granulomatous reaction at the injection site
- Induction of neoplastic changes due to the presence of oncogenic infectious agents or from the action of particular adjuvants

- Disease produced by the presence of infectious agents in live vaccines, undetectable by current conventional methods