

MODULE 2

Types of vaccine and adverse reactions

Overview

There are many types of vaccines. Different types or formulations affect how they are used, how they are stored, and how they are administered. If they are to be safe and effective, it is vital to be familiar with the different types and to know how to handle them.

Different vaccines can cause different adverse reactions, and it is important to recognize what these may be. Can you identify the contraindications for vaccination and know which present an additional risk? What special considerations should you make when immunizing pregnant women or immunocompromised clients?

This module will explain the different types of vaccine and the main routes of administration. You will learn about the main vaccine reactions and the importance of understanding contraindications – as ignoring these could lead to vaccine reactions. Finally, you will look at public concern over vaccines and consider some rumours about vaccine safety that have been disproved by research.

Module outcomes

By the end of this module you should be able to:

- 1 Explain the modes of action of live attenuated vaccines, conjugate vaccines, subunit vaccines, and toxoid vaccines,
- 2 List types of vaccine components, including adjuvants and preservatives, and explain their functions,
- 3 Explain the difference between live attenuated and inactivated vaccines,
- 4 Identify the contraindications for vaccination that may present an additional risk.

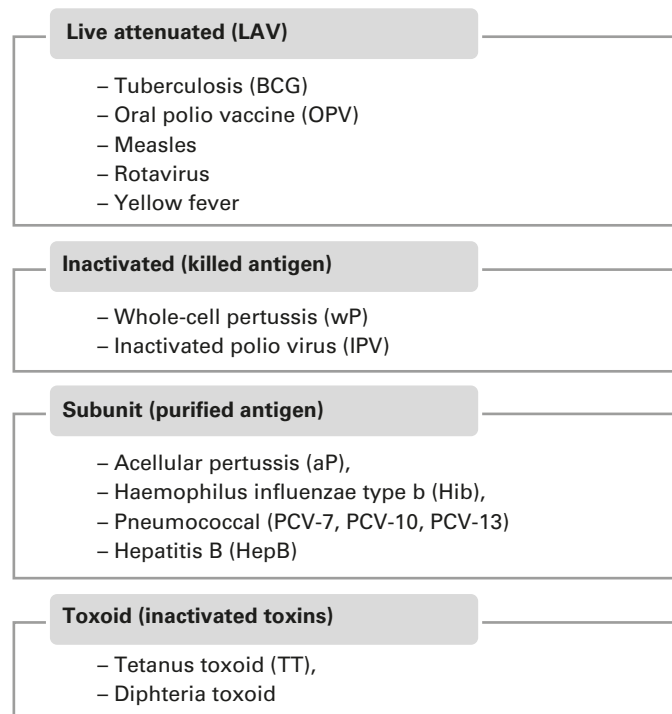
Types of vaccine

In module 1 we have learned that vaccines are used to prevent serious illnesses and that regulatory authorities have strict requirements for safety before they are approved for use.

Vaccines require rigorous follow-up once approved for use to assess types and rates of adverse events. The development of more effective and even safer vaccines as well as developing vaccines for more diseases that are serious is always ongoing.

There are many types of vaccines, categorized by the antigen used in their preparation. Their formulations affect how they are used, how they are stored, and how they are administered. The globally recommended vaccines discussed in this module fall into four main types.

Types of Vaccine



Mono and polyvalent vaccines

Vaccines may be monovalent or polyvalent. A monovalent vaccine contains a single strain of a single antigen (e.g. Measles vaccine), whereas a polyvalent vaccine contains two or more strains/serotypes of the same antigen (e.g. OPV).

Combination vaccines

Some of the antigens above can be combined in a single injection that can prevent different diseases or that protect against multiple strains of infectious agents causing the same disease (e.g. combination vaccine DPT combining diphtheria, pertussis and tetanus antigens). Combination vaccines can be useful to overcome logistic constraints of multiple injections, and accommodate for a children's fear of needles and pain.

Live attenuated vaccines

Available since the 1950s, live attenuated vaccines (LAV) are derived from disease-causing pathogens (virus or bacteria) that have been weakened under laboratory conditions. They will grow in a vaccinated individual, but because they are weak, they will cause no or very mild disease.

BACTERIA

Tuberculosis (BCG)

VIRUS

Oral polio vaccine (OPV)

Measles

Rotavirus

Yellow fever

Immune response

LAVs stimulate an excellent immune response that is nearly as good as compared to an infection with the wild-type pathogen.



Live microorganisms provide continual antigenic stimulation giving sufficient time for memory cell production.

In the case of viruses or intracellular microorganisms where cell-mediated immunity is usually desired, attenuated pathogens are capable of replicating within host cells.

Safety and stability

Since LAVs contain living organisms, there is a degree of unpredictability raising some safety and stability concerns.

- Attenuated pathogens have the very rare potential to revert to a pathogenic form and cause disease in vaccinees or their contacts. Examples for this are the very rare, serious adverse events of:
 - vaccine-associated paralytic poliomyelitis (VAPP) and
 - disease-causing vaccine-derived poliovirus (VDPV) associated with oral polio vaccine (OPV).
- Functional immune systems eliminate attenuated pathogens in their immune response. Individuals with compromised immune systems, such as HIV-infected patients may not be able to respond adequately to the attenuated antigens.
- Sustained infection, for example tuberculosis (BCG) vaccination can result in local lymphadenitis or a disseminated infection.
- If the vaccine is grown in a contaminated tissue culture it can be contaminated by other viruses (e.g. retro viruses with measles vaccine).
- As a precaution, LAVs tend not to be administered during pregnancy. However, the actual potential for fetal damage remains theoretical. For example, numerous studies have demonstrated that accidental rubella vaccination during pregnancy did not result in an increased risk of birth defects.
- LAVs can have increased potential for immunization errors:
 - Some LAVs come in lyophilized (powder) form. They must be reconstituted with a specific diluent before administration, which carries the potential for programmatic errors if the wrong diluent or a drug is used.
 - Many LAVs require strict attention to the cold chain for the vaccine to be active and are subject to programme failure when this is not adhered to.

IMMUNE RESPONSE 	SAFETY AND STABILITY 
<ul style="list-style-type: none"> ◆ Live microorganisms provide continual antigenic stimulation, giving sufficient time for memory cell production. ◆ Attenuated pathogens are capable of replicating within host cells. 	<ul style="list-style-type: none"> ◆ Attenuated pathogens can revert to original form and cause disease. ◆ Potential harm to individuals with compromised immune systems (eg. HIV). ◆ Sustained infection (BCG - local lymphadenitis). ◆ Contamination of tissue culture. ◆ Immunization errors (Reconstitution, cold chain). ◆ Usually not given in pregnancy
Excellent immune response	Less safe compared to inactivated vaccines

Adverse reactions associated with LAVs

Five vaccines that are recommended by WHO are produced using LAV technology which are displayed in the table below:

- Tuberculosis (BCG),
- Oral Polio Vaccine,
- Measles,
- Rotavirus,
- Yellow Fever.

The table lists the rare, more severe adverse reactions of these vaccines. Note the frequency of the adverse reactions to get an idea of how low or high the possibility of an adverse event is. Also read the Comments to understand additional context details on the adverse events.



Question 1*

Which of the following statements is correct (Several answers possible see also table on next page):

- A. Febrile seizures are an uncommon reaction to vaccination with measles.
- B. Compared to giving the first dose of measles vaccine, allergic reactions are less likely to occur during the second dose of measles vaccine.
- C. Live vaccines include BCG, Measles, Rotavirus, Pertussis vaccine and Yellow fever vaccine.
- D. Vaccine associated paralytic poliomyelitis occurs very rarely among vaccines (2–4 cases per 1,000,000 vaccinated persons).

* The answer to all questions can be found at the end of this manual (page 202).

Five WHO recommended vaccines using LAV technology

	Vaccine	Rare, more severe adverse reactions	Frequency	Comment
BACTERIA	Tuberculosis (BCG) ²⁸	Fatal dissemination of BCG infection	very rare at 0.000019–0.000159%	Almost exclusively occurs in inadvertently immunized persons with severely compromised cellular immunity.
		BCG osteitis	very rare	In the past BCG osteitis has been reported in connection with certain vaccine batches but now occurs very rarely.
VIRAL	Oral polio vaccine (OPV) ²⁹	Vaccine- associated paralytic poliomyelitis (VAPP) in vaccinees and their contacts	very rare at 0.0002–0.0004%	An essential component of the global polio eradication campaign despite adverse reactions.
	Measles ³¹	Febrile seizures	uncommon at 0.3%	Adverse reactions, with the exception of allergic anaphylactic reactions, are less likely to occur after receipt of the second dose of measles vaccine.
		Thrombocytopenic purpura	very rare at 0.03%	
		Anaphylaxis	very rare at 0.001%	Allergic reactions to vaccine components including neomycin and the stabilizers gelatine or sorbitol, may follow vaccination.
	Rotavirus ⁶¹	None reported to WHO	–	To date, post-licensure surveillance does not indicate any increased risk of intussusception or other serious adverse reaction associated with the use of current rotavirus vaccines.
	Yellow fever (YF) ⁶²	Hypersensitivity reactions	very rare	Sensitivity to egg, which is commonly used to stabilize the vaccine, may explain at least some of these cases.
Vaccine- associated neurotropic disease (encephalitis)		very rare	Infants seem more susceptible to vaccine-associated neurotropic disease than the YF-vaccinated population at large.	
Vaccine- associated viscerotropic disease		very rare in children at 0.00001%	The elderly seem more susceptible to reaction (very rare at 0.04–0.05%) than the YF-vaccinated population at large.	

Inactivated whole-cell vaccines

Inactivated vaccines are made from microorganisms (viruses, bacteria, other) that have been killed through physical or chemical processes. These killed organisms cannot cause disease.

BACTERIA
Whole-cell pertussis (wP)

VIRUS
Inactivated polio virus (IPV)



Immune response

- Inactivated whole-cell vaccines may not always induce an immune response and the response may not be long lived.
- Several doses of inactivated whole-cell vaccines may be required to evoke a sufficient immune response.

Safety and stability

- Inactivated whole-cell vaccines have no risk of inducing the disease they are given against as they do not contain live components.
- They are considered more stable than LAV vaccines.

The table lists the rare, more severe adverse reactions of these vaccines. Note the frequency of the adverse reactions to get an idea of how low or high the possibility of an adverse event is. Also read the Comments to understand additional context details on the adverse events.

IMMUNE RESPONSE 	SAFETY AND STABILITY 
<ul style="list-style-type: none"> ◆ May not always induce an immune response at first dose. ◆ Response may not be long-lived, requiring several doses of vaccine. <p>Less strong immune response compared to live vaccines</p>	<ul style="list-style-type: none"> ◆ Have no live components, no risk of inducing the disease. ◆ Safer and more stable than LAVs. <p>Excellent stability profile</p>

Adverse reactions associated with inactivated whole-cell vaccines

	Vaccine	Rare, more severe adverse reactions	Frequency	Comment
BACTERIA	Pertussis (wP) ³⁰	Prolonged crying and seizures are uncommon	less than 1%	Minor adverse reactions such as local redness and swelling, fever and agitation are very common with wP vaccines (10–50%).
		Hypotonic, hyporeponsive episodes (HHE) are rare	less than 0.1–0.2%	Although mild with no lasting effect, these reactions have affected the acceptance of wP vaccine in some populations. All wP (or DTwP) vaccines contain aluminium salt as adjuvant and in some cases thiomersal as preservative.
VIRAL	Inactivated polio vaccine (IPV) ²⁹	Vaccine-associated paralytic poliomyelitis (VAPP) in vaccinees and their contacts	None known	Many high-income countries have switched from OPV to IPV, as IPV is considered safer. IPV is more expensive than OPV and an injectable vaccine. Many lower- and middle-income countries use OPV.



Question 2*

Which of the following statements is incorrect?

- A. Inactivated whole-cell vaccines contain “killed” pathogens.
- B. Inactivated whole-cell vaccines can be considered safer than live vaccines, particularly when used in vulnerable groups (immunocompromised persons).
- C. Inactivated whole-cell vaccines can be considered more effective compared to live vaccines.
- D. Inactivated whole-cell vaccines should not be seen as ineffective – the immunization schedule foresees repeated doses to ensure adequate immune responses in patients.

Subunit vaccines

Immune response

- Subunit vaccines, like inactivated whole-cell vaccines do not contain live components of the pathogen. They differ from inactivated whole-cell vaccines, by containing only the antigenic parts of the pathogen. These parts are necessary to elicit a protective immune response.
- This precision comes at a cost, as antigenic properties of the various potential subunits of a pathogen must be examined in detail to determine which particular combinations will produce an effective immune response within the correct pathway.
- Often a response can be elicited, but there is no guarantee that immunological memory will be formed in the correct manner.

Protein-based

Polysaccharide

Conjugate

Safety and stability

Like inactivated vaccines, subunit vaccines do not contain live components and are considered as very safe.

<p>IMMUNE RESPONSE </p> <ul style="list-style-type: none"> ◆ Must determine which combination of antigenic properties will produce an effective immune response with the correct pathway. ◆ A response may be elicited, but with no guarantee that memory will form for future responses. <p style="text-align: center;">Less strong immune response compared to LAVs</p>	<p>SAFETY AND STABILITY </p> <ul style="list-style-type: none"> ◆ Have no live components, no risk of inducing the disease. ◆ Safer and more stable than LAVs. <p style="text-align: center;">Excellent stability profile</p>
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* The answer to all questions can be found at the end of this manual (page 202).

Key point

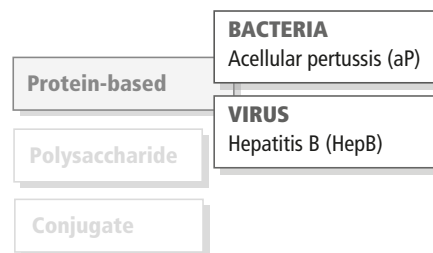
Rather than introducing a whole-cell vaccine (either inactivated or attenuated) to an immune system, a subunit vaccine contains a fragment of the pathogen and elicits an appropriate immune response.

Subunit vaccines can be further categorized into:

- Protein-based subunit vaccines,
- Polysaccharide vaccines,
- Conjugate subunit vaccines.

Protein-based subunit vaccines

Protein based subunit vaccines present an antigen to the immune system without viral particles, using a specific, isolated protein of the pathogen. A weakness of this technique is that isolated proteins, if denatured, may bind to different antibodies than the protein of the pathogen.



Commonly used protein-based subunit vaccines are the following:

- **Acellular pertussis (aP)** vaccines contain inactivated pertussis toxin (protein) and may contain one or more other bacterial components. The pertussis toxin is detoxified either by treatment with a chemical or by using molecular genetic techniques.
- **Hepatitis B** vaccines are composed of the hepatitis B virus surface antigen (HBsAg), a protein produced by hepatitis B virus. Earlier vaccine products were produced using purified plasma of infected individuals. This production method has been replaced by recombinant technology that can produce HBsAg without requiring human plasma increasing the safety of the vaccine by excluding the risk from potential contamination of human plasma.

The table lists the rare, more severe adverse reactions of these vaccines. Note the frequency of the adverse reactions to get an idea of how low or high the possibility of an adverse event is. Also read the Comments to understand additional context details on the adverse events.

Adverse reactions associated with subunit protein-based vaccines

	Vaccine	Rare, more severe adverse reactions	Comment
BACTERIA	Acellular pertussis (aP) ³⁰	Same as tetanus and diphtheria toxoid vaccines.	Acellular pertussis-containing vaccines are less reactogenic in terms of mild-to-moderate reactions than wP-containing vaccines. See "More about Pertussis vaccine".
VIRAL	Hepatitis B (HepB) ⁶³	Very rare	Reports of severe anaphylactic reactions are very rare.

More about Pertussis vaccine

Both acellular (aP) and whole-cell pertussis (wP) vaccines are safe and effective. In terms of rare, more severe adverse reactions, aP and wP vaccines appear to have the same high level of safety. However, mild-to-moderate adverse reactions are more commonly associated with wP vaccines, and tend to increase with client age and the number of injections. This is why wP vaccines are not recommended for use in adolescents and adults where aP vaccines rather come to use.

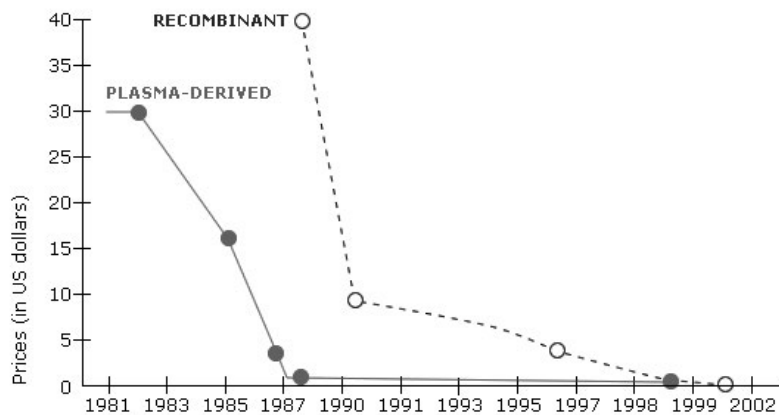
Because the price of wP is considerably less than aP, where resources are limited and the vaccine is well accepted by the local population, wP vaccine remains the vaccine of choice. In countries where a higher rate of adverse reactions after immunization with wP prevents high vaccination coverage, aP is recommended instead, at least for booster injections.³⁰

More about Hepatitis B vaccines

The first available hepatitis B vaccines were plasma-derived, produced by harvesting hepatitis B surface antigen (HBsAg) from the plasma of persons with chronic HBV infection. The particles are highly purified, and any residual infectious particles are inactivated by various combinations of urea, pepsin, formaldehyde and heat. Although concerns about transmission of bloodborne pathogens, including HIV, from plasma-derived vaccines have proven to be unfounded, public concerns over the safety of the plasma-derived vaccine hampered its acceptance in many populations. Therefore increased research efforts were made to develop a recombinant vaccine.

In 1986, a hepatitis B vaccine produced by recombinant technology was licensed, and a second followed in 1989. The recombinant technology expressed HBsAg in other microorganisms and offered the potential to produce unlimited supplies of vaccine.

Although both the plasma-derived and recombinant hepatitis B vaccines are safe and highly effective in protecting against acute hepatitis disease as well as chronic disease, including cirrhosis and liver cancer, competition among the various hepatitis B vaccine producers drove down the price (see figure). When the price of both the plasma-derived and recombinant hepatitis B vaccines was relatively similar, the recombinant gradually replaced the plasma-derived hepatitis B vaccine.



Polysaccharide vaccines

Some bacteria when infecting humans are often protected by a polysaccharide (sugar) capsule that helps the organism evade the human defense systems especially in infants and young children.

Protein-based

Polysaccharide

Conjugate

Polysaccharide vaccines create a response against the molecules in the pathogen’s capsule. These molecules are small, and often not very immunogenic. As a consequence they tend to:

1. Not be effective in infants and young children (under 18–24 months),
2. Induce only short-term immunity (slow immune response, slow rise of antibody levels, no immune memory).

Examples of polysaccharide vaccines include Meningococcal disease caused by *Neisseria meningitidis* groups A, C, W135 and Y, as well as Pneumococcal disease.

Conjugate subunit vaccines

Conjugate subunit vaccines also create a response against the molecules in the pathogen’s capsule. In comparison to plain polysaccharide vaccines, they benefit from a technology that binds the polysaccharide to a carrier protein that can induce a long-term protective response even in infants.

Protein-based

Polysaccharide

Conjugate

BACTERIA
Haemophilus influenzae type b (Hib),
 Pneumococcal (PCV-7, PCV-10, PCV-13)

Various protein carriers are used for conjugation, including diphtheria and tetanus toxoid. Conjugate subunit vaccines, can therefore prevent common bacterial infections for which plain polysaccharide vaccines are either ineffective in those most at risk (infants) or provide only short-term protection (everyone else).

The advent of conjugate subunit vaccines heralded a new age for immunization against diseases caused by encapsulated organisms such as meningococcus, *Haemophilus influenzae* type b (Hib) and pneumococcus.

WHO recommends that children receive *Haemophilus influenzae* type b (Hib) and pneumococcal conjugate vaccines. In addition, the meningococcal A vaccine introduced in Africa is also a conjugated subunit vaccine.

Adverse reactions associated with conjugate vaccines

	Vaccine	Rare, more severe adverse reactions	Comment
BACTERIA	<i>Haemophilus influenzae</i> type b conjugate (Hib) ⁶⁵	None known	Hib vaccine has not been associated with any rare, more severe adverse reactions.
	Pneumococcal conjugate, 7-valent (PCV-7), 10-valent (PCV-10), 13-valent (PCV-13) ⁶⁶	None known	PCV conjugate vaccines have not been associated with any rare, more severe adverse reactions. As with the introduction of any new vaccine, continued surveillance for possible unexpected effects is important.



Key point

Conjugate vaccines can prevent common bacterial infections for which plain polysaccharide vaccines are either ineffective in those most at risk (infants) or provide only short-term protection (everyone else).



Question 3*

Which of the following statements is incorrect:

- A. Polysaccharide vaccines provoke an immune response against the polysaccharide capsule.
- B. Conjugate vaccine binds the polysaccharide to a carrier protein.
- C. Polysaccharide vaccines are targeted, but not very immunogenic. They induce only short-term immunity. Polysaccharide vaccines do not provoke a sufficient immune response in infants and young children but can in adults.
- D. Measles vaccine is a typical example for a Conjugate vaccine that provides better protection for infants compared to a Polysaccharide vaccine.
- E. Conjugate vaccine is effective in those most at risk (infants) and provides longer term protection (everyone else).

Toxoid vaccines

Toxoid vaccines are based on the toxin produced by certain bacteria (e.g. tetanus or diphtheria).

BACTERIA
Tetanus toxoid (TT)
Diphtheria toxoid

The toxin invades the bloodstream and is largely responsible for the symptoms of the disease. The protein-based toxin is rendered harmless (toxoid) and used as the antigen in the vaccine to elicit immunity.

To increase the immune response, the toxoid is adsorbed to aluminium or calcium salts, which serve as adjuvants.

Safety and stability

Toxoid vaccines are safe because they cannot cause the disease they prevent and there is no possibility of reversion to virulence. The vaccine antigens are not actively multiplying and do not spread to unimmunized individuals. They are stable, as they are less susceptible to changes in temperature, humidity and light.⁷⁶

<p>IMMUNE RESPONSE </p> <ul style="list-style-type: none"> ◆ May require several doses and usually need an adjuvant. <p style="text-align: center;">Not highly immunogenic</p>	<p>SAFETY AND STABILITY </p> <ul style="list-style-type: none"> ◆ Vaccine cannot cause disease it prevents. ◆ Very rare local and systemic reactions. ◆ Usually stable and long lasting. <p style="text-align: center;">Excellent stability profile</p>
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* The answer to all questions can be found at the end of this manual (page 202).

Adverse reactions associated with toxoid vaccines

	Vaccine	Rare, more severe adverse reactions	Comment
BACTERIA	Tetanus toxoid (TT) ⁶⁶	Anaphylaxis (1–6 per million) and brachial neuritis (5–10 per million) are extremely rare	Local and systemic reactions increase with increasing number of doses.
	Diphtheria toxoid (DT and Td) ⁶⁹	None known	No anaphylactic reactions attributable to the diphtheria component have been described.

Combination vaccines

Licensed combination vaccines undergo extensive testing before approval by national regulatory authorities to assure that the products are safe, effective, and of acceptable quality.

Combination vaccines consist of two or more antigens in the same preparation. This approach has been used for over 50 years in many vaccines such as DTwP and MMR. Combination products simplify vaccine administration and allow for the introduction of new vaccines without requiring additional health clinic visit and injections.

Potential advantages of combination vaccines include:

- Reducing the cost of stocking and administering separate vaccines,
- Reducing the cost of extra health care visits,
- Improving timeliness of vaccination (some parents and health-care providers object to administering more than two or three injectable vaccines during a single visit because of a child’s fear of needles and pain, and because of concerns regarding safety),
- Facilitating the addition of new vaccines into immunization programmes.

It is very important, however, that combination vaccines are carefully tested before introduction. For instance, adjuvants in a combination vaccine could reduce the activity of one antigen and excessively increase the reactivity of another antigen. There could also be interactions with other vaccine components such as buffers, stabilizers and preservatives.

With all combinations, manufacturers must therefore evaluate the potency of each antigenic component, the effectiveness of the vaccine components when combined to induce immunity, risk of possible reversion to toxicity, and reaction with other vaccine components.



Key point

No evidence exists that the administration of several antigens in combined vaccines overwhelms the immune system, which has the capability of responding to many millions of antigens at a time. Combining antigens usually does not increase the risk of adverse reactions. In fact, it can lead to an overall reduction in adverse reactions.

With all combinations, manufacturers must, however, evaluate the potency of each antigenic component, the effectiveness of the vaccine components when combined to induce immunity, risk of possible reversion to toxicity, and reaction with other vaccine components.



Question 4*

Can you identify which five antigens are included in the pentavalent vaccine DTwPHepBHib?

Components of a vaccine

Vaccines include a variety of ingredients including antigens, stabilizers, adjuvants, antibiotics, and preservatives.

They may also contain residual by-products from the production process. Knowing precisely what is in each vaccine can be helpful when investigating adverse events following immunization (AEFIs) and for choosing alternative products for those who have allergies or have had an adverse event known or suspected to be related to a vaccine component.

Antigens

Antigens are the components derived from the structure of disease-causing organisms, which are recognized as ‘foreign’ by the immune system and trigger a protective immune response to the vaccine.

You have already learned about antigens on the chapter “Types of vaccine”.

Stabilizers

Stabilizers are used to help the vaccine maintain its effectiveness during storage. Vaccine stability is essential, particularly where the cold chain is unreliable. Instability can cause loss of antigenicity and decreased infectivity of LAV. Factors affecting stability are temperature and acidity or alkalinity of the vaccine (pH). Bacterial vaccines can become unstable due to hydrolysis and aggregation of protein and carbohydrate molecules. Stabilizing agents include $MgCl_2$ (for OPV), $MgSO_4$ (for measles), lactose-sorbitol and sorbitol-gelatine.

Adjuvants

Adjuvants are added to vaccines to stimulate the production of antibodies against the vaccine to make it more effective.

Adjuvants have been used for decades to improve the immune response to vaccine antigens, most often in inactivated (killed) vaccines. In conventional vaccines, adding adjuvants into vaccine formulations is aimed at enhancing, accelerating and prolonging the specific immune response to vaccine antigens. Newly developed purified subunit or synthetic vaccines using biosynthetic, recombinant, and other modern technology are poor vaccine antigens and require adjuvants to provoke the desired immune response.

Chemically, adjuvants are a highly heterogeneous group of compounds with only one thing in common: their ability to enhance the immune response. They are highly variable in terms of how they affect the immune system and how serious their adverse reactions are, due to the resulting hyperactivation of the immune system.

* The answer to all questions can be found at the end of this manual (page 202).

Today there are several hundred different types of adjuvants that are being used or studied in vaccine technology.

Aluminium salts example

Aluminium salts are among the oldest adjuvants that are commonly used. They slow the escape of the antigen from the site of injection thereby lengthening the duration of contact between the antigen and the immune system (i.e. macrophages and other antigen-receptive cells).

Aluminium salts are generally recognized as safe, however, they can cause sterile abscesses and nodules at the site of injection. The formation of a small granuloma is inevitable with alum-precipitated vaccines.

To ensure safe vaccination it is important that aluminium salts are administered intramuscularly and not subcutaneously. Subcutaneous administration can result in necrotic breakdown and cyst and abscess formation. To ensure the proper handling of intramuscular injections, it is critical to ensure that vaccination staff has been well trained.

Antibiotics

Antibiotics (in trace amounts) are used during the manufacturing phase to prevent bacterial contamination of the tissue culture cells in which the viruses are grown. Usually only trace amounts appear in vaccines, for example, MMR vaccine and IPV each contain less than 25 micrograms of neomycin per dose (less than 0.000025 g). Persons who are known to be allergic to neomycin should be closely observed after vaccination so that any allergic reaction can be treated at once.

- Used during the manufacturing phase to prevent bacterial contamination of tissue culture cells in which viruses are grown,
- Usually only trace amounts appear in vaccines, for example, MMR and IPV vaccines each contain less than 25 micrograms of neomycin per dose,
- Persons known to be allergic to neomycin should be closely observed after vaccination so any allergic reaction can be immediately treated.

Preservatives

Preservatives are added to multidose vaccines to prevent bacterial and fungal growth. They include a variety of substances, for example Thiomersal, Formaldehyde, or Phenol derivatives.

Thiomersal

- Very commonly used preservative. Thiomersal is an ethyl mercury-containing compound,
- It has been in use since the 1930ies and no harmful effects have been reported for doses used in vaccination except for minor reactions (e.g. redness, swelling at injection site),
- It is used in multidose vials and for single dose vials in many countries as it helps reduce storage requirements/costs,
- Thiomersal has been subjected to intense scrutiny, as it contains ethyl mercury. The Global Advisory Committee on Vaccine Safety continuously review the safety aspects of Thiomersal. So far, there is no evidence of toxicity when exposed to Thiomersal in vaccines. Even trace amounts of thiomersal seem to have no impact on the neurological development of infants.

Formaldehyde

- Used to inactivate viruses (e.g. IPV) and to detoxify bacterial toxins, such as the toxins used to make diphtheria and tetanus vaccines,
- During production, a purification process removes almost all formaldehyde in vaccines,
- The amount of formaldehyde in vaccines is several hundred times lower than the amount known to do harm to humans, even infants. E. g., DTP-HepB + Hib “5-in-1” vaccine contains less than 0.02% formaldehyde per dose, or less than 200 parts per million.



Question 5*

Which of the following answers is incorrect?

- A. Thiomersal prevents bacterial growth and therefore make vaccines more durable, which is particularly helpful for storing and use of multi-dose vials.
- B. Aluminium salts primarily serve to prevent bacterial contamination of tissue culture cells.
- C. Adjuvants serve to enhance the immune response.
- D. Stabilizers make a vaccine more stable towards temporary changes in temperature and pH.

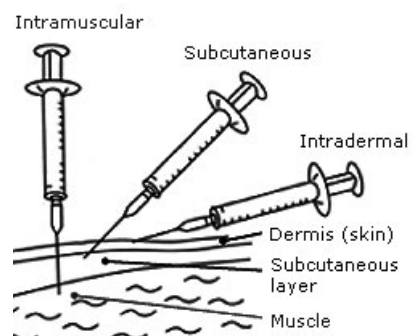
Route of administration

The route of administration is the path by which a vaccine (or drug) is brought into contact with the body. This is a critical factor for success of the immunization. A substance must be transported from the site of entry to the part of the body where its action is desired to take place. Using the body’s transport mechanisms for this purpose, however, is not trivial.

Intramuscular (IM) injection administers the vaccine into the muscle mass. Vaccines containing adjuvants should be injected IM to reduce adverse local effects.

Subcutaneous (SC) injection administers the vaccine into the subcutaneous layer above the muscle and below the skin.

Intradermal (ID) injection administers the vaccine in the top-most layer of the skin. BCG is the only vaccine with this route of administration. Intradermal injection of BCG vaccine reduces the risk of neurovascular injury. Health workers say that BCG is the most difficult vaccine to administer due to the small size of newborns’ arms. A short narrow needle (15 mm, 26 gauge) is needed for BCG vaccine. All other vaccines are given with a longer, wider needle (commonly 25 mm, 23 gauge), either SC or IM.



Oral administration of vaccine makes immunization easier by eliminating the need for a needle and syringe.

Intranasal spray application of a vaccine offers a needle free approach through the nasal mucosa of the vaccinee.

* The answer to all questions can be found at the end of this manual (page 202).

Intranasal flu vaccine

In October 2000, an inactivated intranasal flu vaccine was licensed in Switzerland. Results from a case control study and a case-series analysis indicated a significantly increased risk of Bell's palsy, a one-sided paralysis of facial muscles, developing after intranasal immunization with the vaccine. Following spontaneous reports of Bell's palsy in vaccine recipients, the producer decided not to further market the vaccine.

As a result of the occurrence of Bell's palsy, the Global Advisory Committee on Vaccine Safety (GACVS) recommended additional caution for new intranasal vaccines under development and recommended that the follow-up period in the context of clinical trials should be routinely extended to three months following administration.

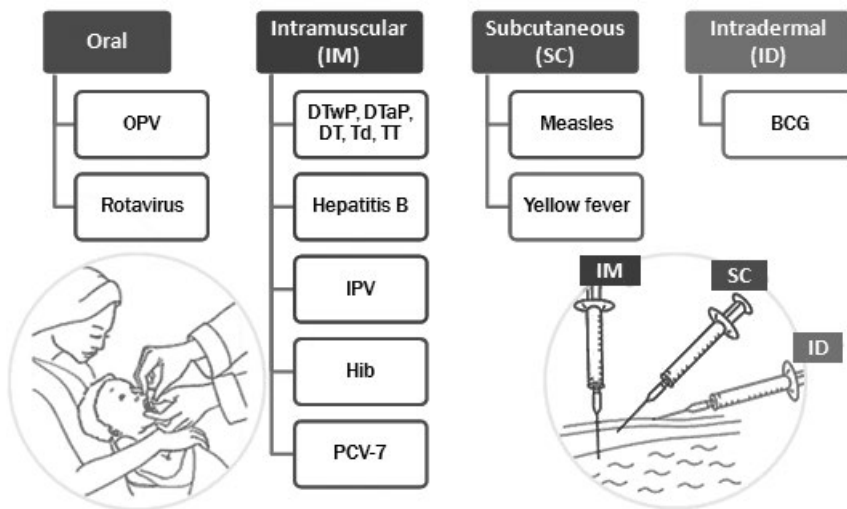
In 2003, a cold attenuated reassortant live intranasal vaccine was licensed in the US. This vaccine differs in formulation and manufacturing from adjuvanted inactivated intranasal vaccine. Bell's palsy was not observed in clinical trials of the cold attenuated reassortant live intranasal vaccine. As of 6 July 2006, with over four million vaccine doses distributed, a total of five Bell's palsy cases have been reported to the adverse event reporting system of the US. A causal association between these reported cases and the vaccine has not been established.

The GACVS continues to review the safety of vaccines administered by the intranasal route.



Bell's palsy (a one-sided paralysis of facial muscles) after intranasal immunization with the vaccine.

Routes of administration vary to maximize effectiveness of vaccine



Key point

- Manufacturers usually recommend the route of administration that limits best adverse reactions of the respective vaccine.

Contraindications




















A contraindication to vaccination is a rare condition in a recipient that increases the risk for a serious adverse reaction. Ignoring contraindications can lead to avoidable vaccine reactions. Most contraindications are temporary, and the vaccination can be administered later.

The only contraindication applicable to all vaccines is a history of a severe allergic reaction after a prior dose of vaccine or to a vaccine constituent. Precautions are not contraindications, but are events or conditions to be considered in determining if the benefits of the vaccine outweigh the risks. Precautions stated in product labelling can sometimes be inappropriately used as absolute contraindications, resulting in missed opportunities to vaccinate.

Signs of allergic reactions

Vaccinating health workers should know the signs of allergic reactions and be prepared to take immediate action.

Contraindications to vaccines

Childhood vaccine	Anaphylaxis after previous dose or severe allergy to vaccine component	Pregnancy	Severely immunocompromised*	Comment
BCG ²⁸				Further information available at http://who.int/vaccine_safety/committee/topics/bcg/immunocompromised/Dec_2006/en/
DTwP ³⁰				
DTaP ³⁰				
OPV ²⁹				
IPV ²⁹				CAVEAT: allergy to neomycin.
Measles ³¹				Severe allergy to gelatine is a contraindication to vaccination with MMR vaccine.
HepB ⁶³				
Rotavirus ⁶¹				
Hib ⁶⁵				
PCV-7 ⁶⁶				
Yellow fever ⁶²				CAVEAT: severe allergy to egg. Contraindicated in infants less than 6 months.

* Includes symptomatic HIV/AIDS (but for most LAV vaccines, asymptomatic or properly treated HIV infection is not a contraindication).

Key point

True contraindications are rare. Misconceptions about their frequency can lead to missed opportunities to vaccinate and decrease immunization coverage, or conversely increase the risk of adverse reactions, both of which reduce public confidence in the safety of the vaccine.

Anaphylaxis

Anaphylaxis is a very rare allergic reaction (one in a million vaccinees), unexpected, and can be fatal if not dealt with adequately. Vaccine antigens and components can cause this allergic reaction. These reactions can be local or systemic and can include mild-to-severe anaphylaxis or anaphylactic-like responses (e.g. generalized urticaria or hives, wheezing, swelling of the mouth and throat, breathing difficulties, hypotension and shock). Reports of anaphylaxis are less common in low- and middle-income countries compared to high-income countries, probably because of reduced surveillance sensitivity and as the event may not be recognized (i.e. death attributed to another factor).


The Brighton Collaboration case definition and guidelines for anaphylaxis are available on their website:

 www.brightoncollaboration.org

Misdiagnosis of faints and other common causes of collapse, such as anaphylaxis, can lead to inappropriate treatment (e.g. use of adrenaline and failure to recognize and treat other serious medical conditions).

Anaphylaxis of unknown cause and unrelated to vaccines increases during adolescence, being more common among girls. Vaccinators should be able to distinguish anaphylaxis from fainting and vasovagal syncope (which is also common in adolescents), as well as anxiety and breath-holding spells, which are all common benign adverse events.

WHO's guidelines on recognition and treatment of anaphylaxis is included in Annex C of Mass Measles Immunization Campaigns: Reporting and investigating adverse events following immunization.⁷¹

 vaccine-safety-training.org/tl_files/vs/pdf/AEFI_measles_campaigns.pdf

Distinguishing anaphylaxis from a fainting (vasovagal reaction)

	Fainting	Anaphylaxis
Onset	Usually at the time or soon after injection	Usually some delay between 5–30 minutes after injection
Symptoms		
Skin	Pale, sweaty, cold and clammy	Red, raised, and itchy rash; swollen eyes, face; generalized rash
Respiratory	Normal to deep breaths	Noisy breathing from airways obstruction (wheeze or stridor)
Cardiovascular	Bradycardia	Tachycardia
	Transient hypotension	Hypotension
Gastrointestinal	Nausea/Vomiting	Abdominal cramps
Neurological	Transient loss of consciousness, good response once prone	Loss of consciousness, little response once prone

Using adrenaline to treat anaphylaxis

Adrenaline stimulates the heart and reverses the spasm in the blood vessels and the lung passages, reduces oedema and urticaria, thus countering the anaphylaxis. But this very potent agent can cause irregular heartbeat, heart failure, severe hypertension and tissue necrosis if used inappropriately, although not when treating true anaphylaxis.

The expiry date of adrenaline should be written on the outside of the emergency kit. Adrenaline that has a brown tinge must be discarded.



Key point

- Each vaccinator who is trained in the treatment of anaphylaxis should have rapid access to an emergency kit with adrenaline, and be familiar with its dosage and administration.

Immunizing the immunocompromised

People may be immunocompromised due to HIV/AIDS, congenital immune deficiencies or drug treatments such as chemotherapy for cancer and other conditions and high dose steroids.

Measles vaccination and HIV infection

Measles in children with HIV infection is more often severe and results in higher mortality. Infants born to HIV-infected mothers are at higher risk for measles from 9 months of age.

Measles vaccines, a live attenuated vaccine, are among the most safe and effective vaccines. They should be given routinely to potentially susceptible, asymptomatic, HIV-infected children, adolescents and young adults. Only those with severe clinical symptoms of HIV infection are contraindicated for vaccination. These people often do not develop a protective immune response and are at increased risk of severe complications.

Given the high risk of measles at 9 months of age, WHO recommends that infants infected with HIV receive an early dose of measles vaccine at 6 months of age, followed by a routine dose at 9 months (or according to the routine immunization schedule). Earlier age of vaccination is recommended because HIV-infected infants exhibit a better seroconversion rate at 6 months than at 9 months of age, possibly because of increasing HIV-associated immunodeficiency with age.

HIV-infected infants vaccinated at 6 and 9 months should receive a third measles vaccination (or second opportunity) to prevent the proportion of unprotected children in the population from reaching dangerous levels. Recent studies suggest waning immunity among HIV-infected children, making this recommendation especially important in regions with high HIV prevalence.³¹

The potential risks of live vaccines need to be weighed against the benefits in immunocompromised clients who may be particularly vulnerable to the vaccine-preventable disease. Concerns are that they may not respond adequately to subunit and inactivated vaccination and that LAV vaccines are potentially pathogenic.

Routine childhood vaccinations – except BCG vaccination⁷² – are not contraindicated in children with asymptomatic HIV-infection; however, timing of vaccination may be earlier or more frequent in this subgroup.

In symptomatic HIV/AIDS, LAV vaccines are contraindicated, e.g. measles and yellow fever vaccines should not be given.

BCG vaccination for infants at risk for HIV infection

As in infants symptoms of HIV-infection rarely appear before several months of age, BCG vaccination should be administered to those infants regardless of HIV exposure, especially considering the high endemicity of tuberculosis in populations with high HIV prevalence.

Close follow-up of infants known to be born to HIV-infected mothers and who received BCG at birth is recommended in order to provide early identification and treatment of any BCG-related complication.

In settings with adequate HIV services that could allow for early identification and administration of antiretroviral therapy to HIV-infected children, consideration should be given to delaying BCG vaccination in infants born to mothers known to be infected with HIV until these infants are confirmed to be HIV negative.

Infants who demonstrate signs or reported symptoms of HIV-infection and who are born to women known to have HIV infection should not be vaccinated.

Immunization and pregnancy

Key point

- No evidence exists of risk from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids.

Influenza



Inactivated influenza vaccine is now recommended for pregnant women in many industrialized countries because of evidence of benefit to the mother and the infant. LAV vaccines pose a theoretical risk to the fetus and are generally contraindicated in pregnant women.

An additional vaccination recommended for pregnant women is seasonal inactivated influenza vaccine. It is considered safe and is recommended for all pregnant women during the influenza season.

This recommendation is motivated not only by the potential severe course of influenza during pregnancy, but also to protect infants against influenza during their vulnerable first months of life⁷³. WHO's Strategic Advisory Committee of WHO (SAGE) has recently discussed seasonal influenza vaccination and recommended pregnant women as the most important risk group for seasonal influenza vaccination. SAGE also supported the recommendation, in no particular order of priority, of vaccination of the following targeted populations:⁷⁷

- Healthcare workers,
- Children 6 to 59 months of age,
- The elderly,
- Those with high-risk conditions.

SAGE Meetings: Information related to influenza immunization:



http://who.int/influenza/vaccines/SAGE_information

Tetanus

Worldwide, all countries are committed to “elimination” of maternal and neonatal tetanus (MNT), i.e. a reduction of neonatal tetanus incidence to below one case per 1000 live births per year in every district. As of 2012, 35 countries have yet to eliminate MNT.

All women of childbearing age, either during pregnancy or outside of pregnancy, should be vaccinated against tetanus to protect themselves and their newborn babies. Neonatal tetanus is almost always fatal and is completely preventable by ensuring that pregnant women are protected through vaccination.

Benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus, and when the vaccine is unlikely to cause harm. This should be assessed on a case-by-case basis.

Tetanus toxoid vaccine example

Tetanus is caused by bacteria that enter the body through open wounds. The bacteria cause an increased tightening of muscles, resulting in spasms, stiffness, and arching of the spine. Ultimately, breathing becomes more difficult, and spasms occur more frequently.

People of all ages can get tetanus. But the disease is particularly common and serious in newborn babies. This is called neonatal tetanus. Most infants who get the disease die. Neonatal tetanus is particularly common in rural areas where most deliveries are at home without adequate sterile procedures. WHO estimated that neonatal tetanus killed about 128,000 babies in 2004.⁷⁴

Tetanus can be prevented by immunizing women of childbearing age with tetanus toxoid, either during pregnancy or before pregnancy. This protects the mother and – through a transfer of tetanus antibodies to the fetus – also her baby.

People who recover from tetanus do not have natural immunity and can be infected again and therefore need to be immunized. To be protected throughout life, an individual should receive three doses of DTP in infancy, followed by a booster containing tetanus toxoid (TT) – at school-entry age (4–7 years), in adolescence (12–15 years), and in early adulthood.

The table below demonstrates the duration of protection against tetanus in women who missed the TT vaccination as infants and then received catch-up immunization during their childbearing years (usually taken to be from 15 to 49 years).

Duration of protection in women after 1–5 doses of TT vaccine

Dose (0.5ml)	When given	Duration of protections
TT1	At first contact with women of childbearing age, or as early as possible in the pregnancy	No protection
TT2	At least 4 weeks after TT1	3 years
TT3	At least 6 months after TT2	5 years
TT4	At least 1 year after TT3	10 years
TT5	At least 1 year after TT4	All childbearing years

Vaccination associations and public concern

Beyond the true vaccine reactions that are well documented and have been illustrated throughout this module, the notion that vaccines could be responsible for serious health problems has led to many allegations and many scientific reviews. Some allegations often based on unfounded rumours or poor science have, at times, profoundly affected the performance of immunization programmes and limited the ability to prevent serious diseases. More on rumours and how to manage can be found in Module 6.



For other health conditions, the scientific evidence available is insufficient to conclude that the association is real, but also insufficient to exclude a link. Systematic study of such conditions can be made difficult as the frequency of a true reaction can be extremely low, or effects would be very mild or they occur many years after vaccination. In recent years, the availability of large computerized databases has allowed testing of many of those potential delayed associations, demonstrating nearly ubiquitously that there is no evidence for a link.

You can learn more about balancing vaccine efficacy and safety of vaccines, and the risks of measles infection versus the risks of the measles vaccine, in Module 1, chapter “*Balancing efficacy and safety*” on page 29.

Summary

You have now completed the learning for this module. These are the main points that you have learned.

- The differences between and the modes of action of live attenuated vaccines, inactivated vaccines, conjugate vaccines, subunit and toxoid vaccines and combined vaccines.
- The correct route of administration for different vaccines.
- The types of vaccine components that exist and their functions.
- The contraindications for vaccination that may present an additional risk.
- The vaccinations that are recommended during pregnancy and the contraindications for pregnant women.
- How to recognize unfounded rumours that affect immunization programmes.

**You have completed Module 2.
We suggest that you test your knowledge!**

ASSESSMENT 2

Question 1

Complete each statement by choosing the correct option from the list below:

1. Live attenuated _____, contains living organisms that have been weakened under laboratory conditions. It stimulates an immune response almost as strong as an infection with _____.
2. Killed antigen vaccines, such as _____, are considered to be very safe and stable and have no risk of _____.
3. Conjugated vaccines such as _____, and pneumococcal conjugate vaccines can provide protection from _____ in infants.
4. Recombinant technology is used to produce protein-based subunit vaccines such as _____, by using other organisms (e.g. yeast cells) to express the desired _____.

- | | |
|---|--|
| a inactivated polio vaccine (IPV) | e wild-type viruses |
| b inducing the disease | f acellular pertussis (aP) vaccines |
| c <i>Haemophilus influenzae</i> type b vaccine (Hib) | g vaccine antigens |
| d common bacterial infections | h measles vaccine |

Question 2

Which of the following statements is correct? Select one or more:

- A. The oral polio vaccine (OPV) never causes paralysis in vaccinated children because the polioviruses in the vaccine have been inactivated.
- B. Live attenuated vaccines may pose a risk to people whose immune system is deficient or suppressed.
- C. Many live attenuated vaccines require strict adherence to the cold chain in order to maintain their efficacy.
- D. Tissue cultures in which live attenuated vaccines are grown may become contaminated with other pathogens.
- E. Live attenuated vaccines induce a weak immune response and therefore always contain adjuvants to enhance the immune response to the vaccine.
- F. Inactivated vaccines are more immunogenic than live attenuated vaccines and a single dose usually produces long-lasting immunity.

Question 3

Which of the following statements is correct? Select one or more:

- A. Live attenuated vaccines include: BCG, OPV, Measles, Rotavirus, whole-cell Pertussis and Yellow fever vaccines.
- B. Osteitis has in the past been reported in connection with certain vaccine batches of BCG vaccines, but now occurs very rarely.
- C. A vaccination with a second dose of a vaccine is contraindicated if a patient previously suffered from anaphylaxis or a severe allergy due to this vaccine or one of its components.
- D. In individuals with symptoms of HIV/AIDS, LAV vaccines are contraindicated.
- E. Conjugate subunit vaccines overcome the problem posed by bacterial pathogens with polysaccharide capsules that protect them from host defences.

Question 4

Complete each statement by choosing the correct option from the list below:

1. Aluminium salts used in vaccines as _____ can occasionally cause a sterile abscess at the injection site.
2. The effectiveness of some live attenuated vaccines can be maintained during storage by the addition of _____.
3. The addition of trace amounts of _____ prevents bacterial contamination of tissue culture cells in which vaccine viruses are grown.
4. Thiomersal is the most common of the _____ used to prevent bacterial and fungal growth in multidose vaccines.
5. The polioviruses used in manufacturing IPV are inactivated by treatment with _____.
6. The immune response to some vaccines is enhanced by the addition of _____.

- | | |
|-----------------------|------------------------|
| a antibiotics | d preservatives |
| b formaldehyde | e stabilizers |
| c adjuvants | |

Question 5

Complete each statement by choosing the correct option from the list below:

1. Vaccines that contain aluminium salts must be administered by _____ injection to reduce the risk of nodule/abscess formation.
2. BCG is the only routine EPI vaccine given to infants by _____ injection.
3. Current rotavirus vaccine should only be given by the _____ route.
4. Combined diphtheria-tetanus-pertussis vaccines should only be given by the _____ route.
5. A needle-free method of giving flu vaccine is administration by _____.
6. Measles vaccine should be injected into the _____ layer.

- | | |
|---------------------------|------------------------|
| a oral | d intradermal |
| b intranasal spray | e intramuscular |
| c subcutaneous | |

You have completed Assessment 2.

Assessment solutions

Question 1

Correct answers:

1. Live attenuated **measles vaccine**, contains living organisms that have been weakened under laboratory conditions. It stimulates an immune response almost as strong as an infection with **wild-type viruses**.
2. Killed antigen vaccines, such as **inactivated polio vaccine (IPV)**, are considered to be very safe and stable and have no risk of **inducing the disease**.
3. Conjugated vaccines such as ***Haemophilus influenzae* type b vaccine (Hib)** and pneumococcal conjugate vaccines can provide protection from **common bacterial infections** in infants.
4. Recombinant technology is used to produce protein-based subunit vaccines such as **acellular pertussis (aP) vaccine**, by using other organisms (e.g. yeast cells) to express the desired **vaccine antigens**.

Question 2

Answers B, C, and D are correct.

Answer A: Polio is among the five vaccines that are recommended by WHO are produced using Live attenuated vaccine technology: Tuberculosis (BCG), Oral Polio Vaccine, Measles, Rotavirus, Yellow Fever.

Answer E: Live attenuated vaccines stimulate an excellent immune response. Adjuvants are therefore not critical elements of them.

(To revise information on Live attenuated vaccines go to the “*Live attenuated vaccines*” on page 41).

Question 3

Answers B, C, D, and E are correct:

Answer A: whole-cell Pertussis is an inactivated vaccine. More information on the “*Inactivated whole-cell vaccines*” on page 44.

Question 4

Correct answers:

1. Aluminium salts used in vaccines as **adjuvants** can occasionally cause a sterile abscess at the injection site.
2. The effectiveness of some live attenuated vaccines can be maintained during storage by the addition of **stabilizers**.
3. The addition of trace amounts of **antibiotics** prevents bacterial contamination of tissue culture cells in which vaccine viruses are grown.
4. Thiomersal is the most common of the **preservatives** used to prevent bacterial and fungal growth in multidose vaccines.
5. The polioviruses used in manufacturing IPV are inactivated by treatment with **formaldehyde**.
6. The immune response to some vaccines is enhanced by the addition of **adjuvants**.

Question 5

Please note that the vaccine must be given by the same route as in the clinical trials that led to its approval.

Correct answers:

1. Vaccines that contain aluminium salts must be administered by **intramuscular** injection to reduce the risk of nodule/abscess formation.
2. BCG is the only routine EPI vaccine given to infants by **intra-dermal** injection.
3. Current rotavirus vaccine should only be given by the **oral** route.
4. Combined diphtheria-tetanus-pertussis vaccines should only be given by the **intramuscular** route.
5. A needle-free method of giving flu vaccine is administration by **intranasal spray**.
6. Measles vaccine should be injected into the **subcutaneous** layer.