Malaysian Society of Infectious Diseases and Chemotherapy

Guidelines for ADULT IMMUNISATION

3rd Edition

Quick Guide

	19-21 yrs	22-26 yrs	27-49 yrs	50-59 yrs	60-64 yrs	≥65 yrs
Influenza*	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap)*	1 dose Tdap, then Td booster every 10 yrs					
Varicella*	2 doses					
Human papillomavirus (HPV) Female*	3 doses					
Human papillomavirus (HPV) Male*	3 doses	3 doses				
Zoster*					1 dose	
Measles, mumps, rubella (MMR)*	1 or 2 doses					
Pneumococcal conjugate (PCV)*	1 dose					
Pneumococcal polysaccharide (PPV)*	1 or 2 doses					1 dose
Meningococcal*	1 or more doses					
Hepatitis A*	2 doses					
Hepatitis B*	3 doses					
Haemophilus influenzae type b (Hib)*	1 or 3 doses					

For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection; zoster vaccine recommended regardless of prior episode of zoster

Recommended if some other risk factor is present (eg, on the basis of medical, occupational, lifestyle, or other)

No recommendation

*Please refer to the relevant sections for more details

Malaysian Society of Infectious Diseases and Chemotherapy

Guidelines for ADULT IMMUNISATION

3rd Edition

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EDITORIAL PANEL

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Introduction

Immunisation against infectious diseases has been primarily directed towards infants, children and adolescents and has become a routine practice in paediatrics. In many countries, including Malaysia, adult immunisation is not commonly practiced. There is a lack of awareness of the benefits of immunisation for adults, even though there is considerable morbidity and mortality within this age group due to vaccine-preventable diseases.

Adults need vaccination for various reasons:

1. Vaccination helps adults to stay healthy. There are certain infections like influenza, invasive pneumococcal disease and chickenpox that can cause significant morbidity and mortality in adults.

2. Vaccination helps to protect family members and the community from infectious diseases. Adults are an important source of pertussis in very young infants where the infection may be severe and life-threatening.

3. Immunity derived from vaccination during childhood can wane over time; so adults would require boosters of these vaccines.

4. Some adults can face greater risks to certain infections because of their work, travel or underlying diseases.

The primary objective for developing these clinical practice guidelines on adult immunisation is to assist doctors and the public in making decisions on the appropriate use of vaccines in the adult population (defined as those 18 years and above). These recommendations on adult immunisation are evidence-based, appropriate to the Malaysian context and reflect current best practices.

Groups of adults who are at a higher risk of contracting specific infections by virtue of their age, underlying diseases or occupation, are identified and recommendations made for the appropriate vaccines. It is hoped that the judicious use of vaccines will provide a cost-effective way of reducing the

burden of morbidity and mortality due to vaccine-preventable infections among adults in Malaysia.

This is the third edition of the Guidelines For Adult Immunisation and we hope that it will provide a useful resource for all doctors in Malaysia.

Victor Lim
Editor
September 2020

Contraindications and Special Considerations

All vaccines are contraindicated in those who have had a confirmed anaphylactic reaction to:

- a previous dose of a vaccine containing the same antigens, or
- another component contained in the relevant vaccine, e.g. neomycin, streptomycin or polymyxin B (which may be present in trace amounts in some vaccines).

Live vaccines may be temporarily contraindicated in individuals who are:

- immunosuppressed
- pregnant

Some vaccines are contraindicated in specific groups:

- Egg allergy: As of 2017, it has been recommended that egg allergic individuals may be safely vaccinated with the measles mumps rubella (MMR), the measles mumps rubella varicella (MMR-V) vaccine (which contains no egg protein) and the influenza vaccine (which may contain minute traces of egg protein).

  Special precautions such as split dosing, prior allergy testing with the vaccines, allergy specialist review before vaccination or prolonged waiting times after administration are **not required.**

  The yellow fever and Q fever vaccines potentially contain higher amounts of egg protein and an allergy specialist evaluation is recommended before vaccination.

- Severe latex allergy: While it is theoretically possible that latex protein in the tip cap and/or rubber plunger or vial stoppers may cause allergic reactions, there is little evidence that such a risk exists and any such risk

would be extremely small (around 1 per 1 million vaccine doses). Even so, as a precaution, vaccines supplied in vials or syringes that contain latex should not be administered, unless the benefit of vaccination outweighs the risk of an allergic reaction to the vaccine.

For latex allergies other than anaphylactic allergies (e.g. a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain latex can be administered.

- Pregnancy: There is no evidence that any live vaccine (including rubella and MMR) causes direct foetal injury or birth defects. However, since the theoretical possibility of foetal infection still exists, live vaccines should generally be delayed until after delivery. Women should avoid conception for 4 weeks after vaccination with live vaccines. Termination of pregnancy following inadvertent immunisation is not recommended.

  Even though inactivated vaccines cannot replicate and cause infection in either the mother or the foetus, they should be administered to pregnant women only if protection is required without delay.

- Immunosuppression: Live vaccines can, in some situations, cause severe or fatal infections in immunosuppressed individuals (including the HIV-infected) due to extensive replication of the vaccine strain. For this reason, severely immunosuppressed individuals (see section on Immunocompromised Patients on page 248) should not be given live vaccines.

  Killed or recombinant vaccines and toxoids may be administered to immunosuppressed individuals since they cannot replicate. Since they may elicit a lower immune response than in immunocompetent individuals, a double dose may be required.

Other Considerations:

- Adults on stable long term low dose corticosteroid therapy (up to 20mg prednisolone per day for more than 14 days) either alone, or in combination

with other low dose immunosuppressive drugs or low dose non-biological oral immune modulating drugs (e.g. methotrexate, azathioprine, 6-mercapto (purine), are not considered sufficiently immunosuppressed. These patients can therefore receive live vaccines.

- Non-systemic corticosteroids, such as aerosols or topical or intra-articular preparations, do not cause systemic immunosuppression. Neither does replacement schedule of corticosteroids for people with adrenal insufficiency. Therefore, administration of live vaccines is not contraindicated.

Live vaccines should not be given to the following:

- Patients receiving immunosuppressive treatment including radiotherapy or systemic high-dose steroids.

- Patients with evidence of primary or secondary immunodeficiency.

Contact with an individual with immunodeficiency, on current/recent immunosuppressive therapy:

- Historically, smallpox and oral polio were contraindicated in healthy household contacts of immunocompromised patients.

- For most of the current live vaccines in use, transmission through contacts does not occur or can be minimised by simple precautions (e.g. MMR, varicella. See vaccine specific advice).

- In addition, vaccination of close contacts of vulnerable people has a major benefit by reducing the risk of exposure to wild-type infection. Thus, some vaccines should be actively encouraged in family and household contacts of those at risk.

- Organ transplant candidates should complete the recommended full vaccination schedule as early as possible because of the problem of reduced immune response to vaccines following transplantation as a result of immunosuppressive treatment.

Temporary Deferral of Immunisation

The following are situations where temporary deferral of immunisation is required:

- Individuals with immunosuppression from malignant disease on chemotherapy should not receive live attenuated vaccines until at least 3 months after chemotherapy has finished.
- Patients who received a hematopoietic stem cell transplant may be given inactivated vaccine or toxoid from 6 to 12 months after completing all immunosuppressive treatment, or longer if the patients developed graft versus-host disease.
- For those on high dose systemic corticosteroids (for adults; daily doses in excess of 20mg for more than 2 weeks or 60mg of prednisolone), live attenuated vaccines should be postponed until at least 3 months after treatment has stopped.
- Live virus vaccines, with the exception of yellow fever vaccine, generally should not be given during the 3 months following injection of immunoglobulin because the immune response may be inhibited. For MMRV vaccine, refer to Table 10.1 on page 113.

The following are NOT contraindications to routine vaccinations (in some of these situations, additional precautions may be required – refer to the relevant chapter for further information):

- Minor self-limiting illness without fever.
- Asthma, eczema, or hay fever.
- Treatment with antibiotics or locally-acting (e.g. topical or inhaled) steroids.
- Contact with an infectious disease.

- Family history of any adverse reactions following immunisation.
- Previous history of the disease (with the exception of BCG for people who have evidence of past exposure to tuberculosis).
- Someone in the household being pregnant.
- Personal or family history of febrile convulsions or epilepsy.
- Being a sibling or close contact of an immunosuppressed individual.
- Recent or imminent elective surgery.
- Imminent general anaesthesia.
- Unknown or inadequately documented immunisation history.
- Food intolerances.
- Treatment with interferons & other non-immunosuppressing immunomodulators.

Route and Site of Administration

By mouth :

- Sugar lumps, if used, should be prepared with oral polio vaccine (OPV) immediately before administration. By allowing them to stand at room temperature for any length of time, may decrease the potency of the vaccine.
- Cholera and typhoid vaccines are also to be given orally. Food and drink should be avoided for 1 hour before and 1 hour after vaccination. Oral administration of other medicinal products should be avoided within 1 hour before and after administration of the vaccine.

Intranasal (Currently no intranasal vaccines are available in Malaysia):

- The live attenuated influenza vaccine (LAIV) is administered by the intranasal route (**Fluenz**®) and is supplied in an applicator that allows a divided dose to be administered in each nostril (total dose of 0.2ml, 0.1ml in each nostril). The device allows intranasal administration to be performed without the need for additional training.

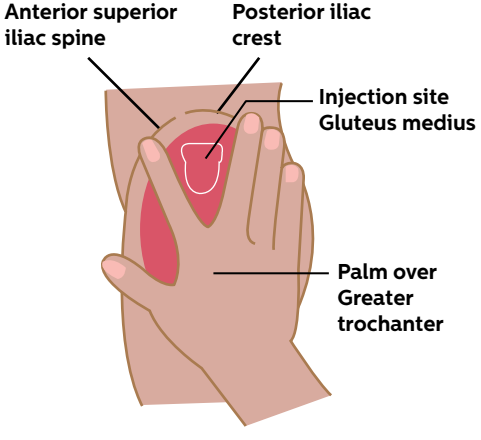
- Administration of either dose does not need to be repeated if the patients sneeze or blow their nose following administration. As heavy nasal congestion might impede delivery of the vaccine to the nasopharyngeal mucosa, defer administration of the vaccine until resolution of the nasal congestion has occurred. Alternatively, an appropriate intramuscularly administered influenza vaccine should be considered.

Subcutaneous (SC) and intramuscular (IM) injections:

- Most vaccines are given by IM injections, rather than deep SC, as the former are less likely to cause local reactions. However, for individuals with a bleeding disorder, vaccines normally given by an IM route should be given by deep subcutaneous injection to reduce the risk of bleeding. **Vaccines should never be given intravenously.**

- The preferred site for IM and SC immunisation is the deltoid area of the upper arm. The upper outer quadrant of the buttock (ventrogluteal) area is an alternative injection site.

Ventrogluteal Site



- IM injections should be given with the needle at a 90^0 angle to the skin and the skin should be stretched, not bunched. Deep SC injections should be given with the needle at a 45^0 angle to the skin and the skin should be bunched, not stretched. It is not necessary to aspirate the syringe after the needle is introduced into the muscle. (refer to Figure 1.1a & b on page 17).

- Immunisations should not be given into the buttock, due to the risk of sciatic nerve damage and the possibility of injecting the vaccine into fat rather than muscle. Injection into fatty tissue of the buttock has been shown to reduce the immunogenicity of hepatitis B and rabies vaccines.

- Inadvertent SC injection of IM vaccines:

  » If a vaccine that is registered for IM administration is inadvertently given subcutaneously, check the vaccine product information and the relevant disease-specific chapters for more details.

  » This can increase the risk of significant local adverse events, particularly with aluminium-adjuvanted vaccines (e.g. HBV, DTPa, DTPa combination or DT vaccines).

  » Hepatitis B vaccines should usually be repeated if they are inadvertently given subcutaneously.

  » Some IM vaccines may still be immunogenic when given by the SC route. These vaccine doses do not need to be repeated

Intradermal injections:

- BCG vaccine is ALWAYS given intradermally. The preferred site of injection is over the insertion of the left deltoid muscle; the tip of the shoulder must be avoided because of the increased risk of keloid formation at this site. For the tuberculin test, the middle flexor surface of the forearm is the recommended site.

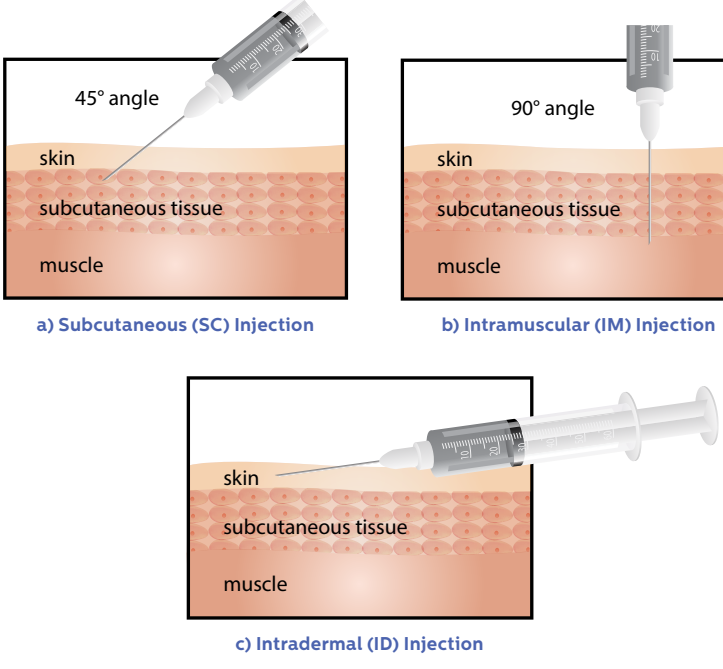
- The BCG technique is specialised and the person giving the BCG vaccine requires specific training and assessment. The skin should be stretched

between the thumb and forefinger of 1 hand and the needle inserted with the bevel upwards for about 2mm into the superficial layers of the dermis, almost parallel with the surface. The needle should be visible beneath the surface of the skin.

- Whilst the IM route is preferred for rabies pre-exposure prophylaxis, suitably qualified and experienced healthcare professionals may give the vaccine via the intradermal route. The preferred site of administration is behind the posterior border of distal portion of deltoid muscle.

- During an intradermal injection, considerable resistance is felt and a raised, blanched bleb showing the tips of the hair follicles is a sign that the injection has been correctly administered. A bleb of 7mm in diameter is approximately equivalent to 0.1ml and is a useful indication of the volume that has been injected. If no resistance is felt, the needle should be removed and reinserted before more vaccine is given (refer to Figure 1.1c).

Figure 1.1 Techniques of Administration



a) Subcutaneous (SC) Injection

b) Intramuscular (IM) Injection

c) Intradermal (ID) Injection

Table 1.1
Injection Routes for Common Vaccines

Vaccines	Dose	Route
Diphtheria, tetanus, pertussis (DTaP, DT, Tdap, Td)	0.5mL	IM
Haemophilus influenzae type b (Hib)	0.5mL	IM
Hepatitis A (Hep A)	≤18 yrs: 0.5mL >18 yrs: 1.0mL	IM
Hepatitis B (Hep B)	<20 yrs: 0.5mL ≥20 yrs: 1.0mL	IM
Human papillomavirus (HPV)	0.5mL	IM
Influenza, quadrivalent inactivated (QIV)	0.5mL	IM
Measles, mumps, rubella (MMR)	0.5mL	SC
Meningococcal conjugate (MCV)	0.5mL	IM
Meningococcal polysaccharide (MPSV)	0.5mL	SC
Pneumococcal conjugate (PCV)	0.5mL	IM
Pneumococcal polysaccharide (PPV)	0.5mL	IM or SC
Polio, inactivated (IPV)	0.5mL	IM or SC
Rotavirus (RV)	2.0mL	Oral
Varicella (Var)	0.5mL	SC
Zoster (Zos)	0.65mL	SC
Combination Vaccines		
DTaP + Hib + IPV	0.5mL	IM
DTaP + Hib		
DTaP + IPV		
HepA + HepB	≥18 yrs: 1.0mL	IM

Note: Always refer to the package insert included with each biologic for complete vaccine administration information.

Table 1.2
Injection Sites and Needle Sizes Appropriate for Each Age Group

Subcutaneous (SC) injection **Use a 23-25 gauge needle. Choose the injection site that is appropriate to the person's age and body mass.**		
Age	**Needle Length**	**Injection Site**
Infants (1-12 mos)	5/8 in	Fatty tissue over anterolateral thigh muscle
Children (12 mos or older), adolescents, and adults	5/8 in	Fatty tissue over anterolateral thigh muscle or fatty tissue over triceps
Intramuscular (IM) Injection **Use a 22-25 gauge needle. Choose the injection site and the needle length appropriate to the person's age and body mass.**		
Age	**Needle Length**	**Injection Site**
Newborns (1st 28 days)	5/8 in*	Anterolateral thigh muscle
Infants (1-12 mos)	1 in	Anterolateral thigh muscle
Toddlers (1-2 yrs)	1 - 1 1/4 in 5/8 - 1 in*	Anterolateral thigh muscle or deltoid muscle of arm
Children & teens (3-18 yrs)	5/8 - 1 in* 1 - 1 1/4 in	Deltoid muscle of arm or anterolateral thigh muscle
Adults (19 yrs or older)		
Male or female less than 59kg	5/8 - 1 in*	Deltoid muscle of arm
Female 59-92kg Male 59-118kg	1 - 1 1/2 in	Deltoid muscle of arm
Female over 92kg Male over 118kg	1 1/2 in	Deltoid muscle of arm

*** A 5/8 in needle may be used only if the skin is stretched tight, subcutaneous tissue is not bunched, and injection is made at a 90° angle.**

Suitable sites for immunoglobulin administration:

- This should be administered deep into a large muscle mass. If the volume is more than 5ml when given to older children and adults, the immunoglobulin should be divided into smaller amounts and given into different sites. The preferred site of injection is the upper outer quadrant (that is, ventrogluteal site) of the buttock.
- Rabies immunoglobulin should be infiltrated into the site of the wound

Interruption to vaccination:

- If the process of administering a vaccine intramuscularly or subcutaneously is interrupted (such as by syringe–needle disconnection) and **most** of the dose has not been given, repeat the whole dose as soon as practicable.

Post Vaccination

- Recipients of vaccine should remain in the vicinity for at least 15 minutes until they have been seen to recover from the procedure. The area should be close enough so that the vaccinated person can be observed and medical treatment can be provided rapidly if needed.
- Paracetamol is not routinely used before, or at the time of, vaccination, but may be recommended as required for fever or pain occurring following immunisation.
- The most serious immediate adverse effect following vaccination is anaphylaxis. However, in adults and older children, the most common immediate adverse event is a vasovagal episode (fainting), either immediately or soon after vaccination. Because this can lead to serious consequences, anyone who complains of giddiness or light-headedness before or after vaccination should be advised to lie down until free of symptoms.

Anaphylaxis

Symptoms of anaphylaxis include:

- Pallor, limpness and apnoea.
- Upper airway obstruction: hoarseness and stridor as a result of angioedema.
- Lower airway obstruction: subjective feelings of retrosternal tightness and dyspnoea with audible expiratory wheeze from bronchospasm.
- Cardiovascular: sinus tachycardia, profound hypotension in association with tachycardia; severe bradycardia.
- Skin: rapid development of urticarial lesions – circumscribed, intensely itchy wheals with erythematous raised edges and pale blanched centres.

Management of anaphylaxis:

- Lie the patient in a left lateral position. If unconscious, insert airway.
- Give 1:1000 (1-in-1,000) adrenaline by deep intramuscular injection unless there is a strong central pulse and the patient's condition is good.
- Adrenaline is not required for generalised non-anaphylactic reactions (such as skin rash or angioedema). If in doubt, IM adrenaline should be given. No serious or permanent harm is likely to occur from mistakenly administering adrenaline to an individual who is not experiencing anaphylaxis.
- For adults, the dosage is 0.5-1.0-mL repeated as necessary up to a maximum of 3 doses. The lower dose should be used for the elderly or those of slight build.
- If oxygen is available, give it by face mask.
- Never leave the patient alone.

- If appropriate, begin cardio-pulmonary resuscitation (CPR).
- Chlorpheniramine maleate 2.5-5.0mg may be given intravenously. Hydrocortisone 100mg may also be given intravenously to prevent further deterioration in severely affected cases.
- If there is no improvement in the patient's condition in 5 minutes, repeat the dose of adrenaline every 5 minutes up to a maximum of 3 doses or until improvement occurs.
- All cases should be admitted to hospital for further observation and treatment.

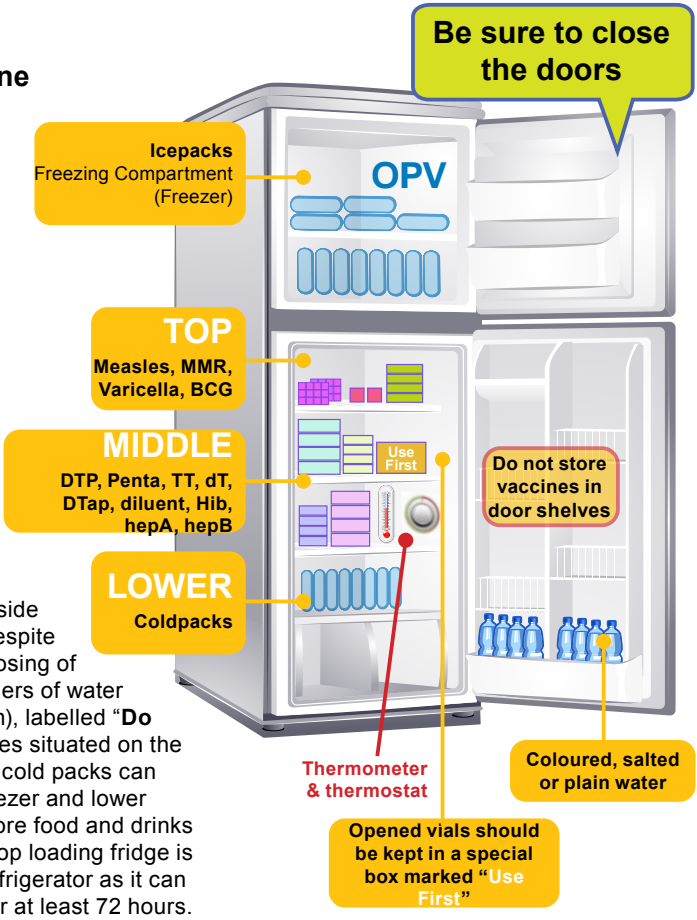
Storage and Disposal of Vaccines

- On receipt, vaccines are immediately placed under the required storage conditions. Vaccines should be stored in the original packaging, retaining batch numbers and expiry dates. Vaccines should be stored according to the manufacturer's summary of product characteristics (SPC) – usually at 2-8°C and protected from light. Generally vaccines should not be kept frozen but there are some exceptions, e.g. Varicella containing vaccines. This causes deterioration or loss of vaccines and may give rise to a loss of potency and an increase in reactogenicity.
- A maximum/minimum thermometer (Minimax), should be used in refrigerators where vaccines are stored, irrespective of whether the refrigerator incorporates a temperature indicator dial. Opening of the refrigerator door should be kept to a minimum in order to maintain a constant temperature. The fridge temperature gauge should be clearly visible to read without needing to open the fridge door. The temperature of the fridge should be measured at least twice a day even during the weekend or a public holiday. The door and drawers of fridges should be filled with bottles of water to maintain steady temperatures.
- Within the refrigerator, sufficient space around the vaccine packages

should be left for air to circulate. Vaccines should be kept away from the side and back walls of the refrigerator; otherwise the vaccines may freeze rendering them inactive and unusable (refer to Figure 1.2 showing appropriate vaccine storage in a designated refrigerator).

- Special care should be taken when bringing the vaccine to room temperature to ensure that the temperature of the vaccine does not exceed the specified range. An insulated container with an appropriate number of ice packs should be used to keep the temperature between 2–8°C.

Figure 1.2
Appropriate Vaccine Refrigeration and Storage



Note: It is important to keep the temperature inside the refrigerator stable despite frequent opening and closing of the doors. Place containers of water (coloured, salted or plain), labelled "**Do NOT Drink**" in the shelves situated on the door. Extra ice packs or cold packs can also be stored in the freezer and lower compartment. Do not store food and drinks inside the refrigerator. Top loading fridge is preferred to domestic refrigerator as it can preserve temperature for at least 72 hours.

- Reconstituted vaccine must be used within the recommended period, varying from 1-4 hours, according to the manufacturer's instructions. Single dose containers are preferable. Once opened, multi-dose vials must not be kept after the end of the session and any unopened vaccine left unused must be discarded unless the temperature is at 2-8°C at all times. The reason is that opened vaccines, especially live vaccines, may have reduced potency and there is also the risk of possible contamination. Thus, it is recommended that multi-dose vials be used for mass vaccination campaigns.

- Immunoglobulins should be stored in the original packaging at 2-8^{0}C and protected from light. Although these products have a tolerance of ambient temperatures (up to 25^{0}C) for up to one week, they should be refrigerated immediately on receipt.

- Unused vaccine, spent or partly spent vials, should be disposed of safely, preferably by heat inactivation or incineration. Contaminated waste and spillage should be dealt with appropriately with heat sterilisation, incineration or chemical disinfection.

Vaccine Combinations

This is becoming more common since it will reduce the number of injections and thus increase compliance. Examples of licensed combination vaccines are highlighted in the separate sections on the individual vaccines.

Problems of combination:

- Side effects may be more frequent and worse.

- Reduced antibody response due to interference.

Multiple Vaccinations

Simultaneous administration on same day:

- No contraindications to simultaneous administration of live attenuated vaccines with inactivated or toxoid vaccines.
- The vaccines should never be mixed in the same syringe unless approved for mixing by the manufacturer.
- Separate sites should be used for different vaccines. If more than 1 vaccine must be administered in the same limb, the injection sites should be separated by 2.5–5.0cm so that any local reactions can be differentiated.

  The location of each injection should be documented in the patient's health record.

Interval between vaccines not administered simultaneously:

- There is no minimum interval between administration of inactivated or toxoid vaccines, or between inactivated and live attenuated vaccines.
- However, 2 or more live vaccines should either be given concurrently or separated by a minimum interval of 4 weeks.

Vaccines and Immunoglobulin preparations:

- If a vaccine and an immunoglobulin preparation are administered simultaneously, a separate anatomic site should be used for each injection.
- If the vaccine and the immunoglobulin preparation are not administered simultaneously, the vaccine and the immunoglobulin should be separated by a minimum interval (refer to Table 1.3 on page 26)

Table 1.3
Intervals Between Vaccines and Immunoglobulin Preparations Not Administered Simultaneously

Vaccine Products	Interval
Between live vaccine and immunoglobulin	2 weeks
Between immunoglobulin and live vaccine	3 months
Between inactivated vaccine and immunoglobulin	6 weeks

With the recent availability of 2 live vaccines not given by a parenteral route (live attenuated nasal influenza vaccine and oral rotavirus vaccine), the guidance to either administer the vaccines on the same day or at 4 week interval period should not be generalised to all live vaccines. Intervals between vaccines should be based only upon specific evidence for any interference of those vaccines.

Table 1.4
Recommendations for Giving More Than One Live Attenuated Vaccine

Vaccine Combinations	Recommendations
Yellow Fever and MMR	4 weeks minimum interval period. Should **not** be administered on the same day
Varicella (and zoster) vaccine and MMR	If these vaccines are not administered on the same day, a 4-week minimum interval should be observed between vaccines.
Mantoux test and MMR	If a tuberculin skin test has already been initiated, then MMR should be delayed until the skin test has been read unless protection against measles is required urgently. If a recent MMR was given, and requires a tuberculin test, then a 4-week interval should be observed.
All currently live vaccines and Mantoux test	Apart from those combinations listed above, these live vaccines and Mantoux test can be administered at any time before or after each other.

Spacing of Multiple Doses of the Same Antigen:

- Administration of doses of a multidose vaccine using intervals that are shorter than recommended might be necessary in certain circumstances, such as
  - » impending international travel,
  - » when a person is behind schedule on vaccinations but needs rapid protection.

- Administering a dose a few days earlier than the minimum interval is unlikely to have a substantially negative effect on the immune response.

- Vaccine doses administered ≤4 days (grace period) before the minimum interval are considered valid. Because of the unique schedule for rabies vaccine, the 4-day guideline does not apply to this vaccine.

- Doses of any vaccine administered ≥5 days earlier than the minimum interval should not be counted as valid doses and should be repeated. The repeat dose should be spaced after the invalid dose by the recommended minimum interval.

- For example, if the first and second doses of hepatitis A vaccine were administered less than 6 months apart, the second dose is invalid and should be repeated 6 months after the invalid second dose. However, if this repeat dose (the third dose) is administered anytime 6 months or more after the first dose, the series can be considered complete.

- Regarding **lapsed vaccination schedule**, intervals between doses that are longer than recommended typically do not reduce final antibody concentrations, although protection might not be attained until the recommended number of doses has been administered. With some exceptions (e.g. oral typhoid vaccine) an interruption in the vaccination schedule does not require restarting the entire series of a vaccine or toxoid or addition of extra doses.

Interchangeability of Formulations:

- A combination vaccine may be used interchangeably with monovalent formulations and other combination products with similar component antigens produced by the same manufacturer to continue the vaccination series.

- For example, DTaP, DTaP-IPV/Hib, and DTaP-HepB-IPV vaccines that contain similar acellular pertussis antigens from the same manufacturer may be used interchangeably.

Interchangeability of Combination Vaccines from different manufacturers:

- It is preferable that doses of vaccine in a series come from the same manufacturer.

- If this is not possible or if the manufacturer of doses given previously is unknown, providers should administer the vaccine that they have available.

Adverse Event Following Immunisation (AEFI)

- An adverse event following immunisation (AEFI) is any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptoms or disease. Reported adverse events can either be true adverse events, ie, really a result of the vaccine or immunisation process, or coincidental events that are not due to the vaccine or immunisation process but are temporally associated with immunisation.

- A serious event is defined by World Health Organization (WHO) as resulting in death, requires hospitalisation or prolongation of existing hospitalisation, persistent or significant disability, life-threatening or causing congenital abnormalities.

- Malaysia has an established AEFI reporting system for vaccines by the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. All reports received will be assessed for causality and presented in the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC), the advisory committee to the Drug Control Authority, for confirmation prior to submission to WHO. Malaysia, as a WHO Collaboration Centre, has been part of the International Drug Monitoring Programme since 1990.

- Methods for reporting

  To report an adverse event following immunisation (AEFI), healthcare professionals can contact the National Centre for Adverse Drug Reaction Monitoring, National Pharmaceutical Regulatory Agency (NPRA):

  - **Kindly report AEFI through only ONE channel:**
    - » PhIS version 1.7 & above* (for Ministry of Health only), **OR**
    - » online web form via this link - https://quest3plus.bpfk.gov.my/front-end/adr_web_form_mid.php, **OR**
    - » manual submission by mail/fax/e-mail by downloading the form via this link - https://www.npra.gov.my/images/Healthcare-professional/reporting/ADR_Form_Healthcare_Prof_web.pdf

  All manual forms to be submitted via the following mode

  a. By facsimile: 03-79567151

  b. Through mail to:

  NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING
  National Pharmaceutical Regulatory Agency
  Lot 36, Jalan Universiti,
  46730 Petaling Jaya, Selangor, Malaysia

  c. By email : fv@npra.gov.my

Repeated submission using multiple channels is NOT necessary.
**Note: If your facility is equipped with PhIS version 1.7 & above, your PhIS ADR report will be automatically pushed to NPRA. For any enquiries related to PhIS reporting, please contact PhIS Helpdesk.*

The National Pharmaceutical Regulatory Agency has developed a Guideline for Pharmacovigilance of Vaccines in Malaysia available at the official website: http://npra.moh.gov.my Please refer to the guideline for further details.

References

1. Advisory Committee on Immunisation Practices. (2020) Recommended Immunisation Schedule for Adults Aged 19 Years or Older-United States, 2020 [Annual Report]. U.S. Centre for Disease Control. http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf
2. Australian Immunisation Handbook (11th ed) 2018 (updated 27 May 2020). Retrieved 14 October 2020, from https: //www.immunisationhandbook.health.gov.au
3. Australian Society of Clinical Immunology and Allergy (2017) Guidelines on Vaccination of the egg-allergic individual. Retrieved 14 October 2020, from www.allergy.org.au
4. Dreskin SC, Halsey NA, Kelso JM, Wood RA, Hummell DS, Edwards KM, et al. (2016). International Consensus (ICON): allergic reactions to vaccines. World Allergy Organization Journal, 9:32. http://dx.doi 10.1186/s40413-0160120-5
5. Epidemiology and Prevention of Vaccine-Preventable Diseases (13th ed) 2015 (updated July 2020) Retrieved 14 October 2020, from http://www.cdc.gov/vaccines/pubs/pinkbook/downloads
6. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP) (2017) Retrieved 14 October 2020, from www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf
7. Immunisation Guidelines (2006). Dubai Health Authority, Dubai. Retrieved 14 October 2020, from www.dha.gov.ae
8. Mary Ramsay (Ed). Immunisation against Infectious Diseases (2017). Public Health England (latest update January 2020) Retrieved 14 October 2020, from www.gov.uk>collections

Cholera

Introduction

Cholera is an important public health problem globally and results in an estimated 2.9 million cases of disease and 95,000 deaths annually. Cholera is endemic in Malaysia with incidence rate ranged between 0.01-0.8 per 100,000 population in the last five years (2014-2019). High incidence rates in 2015 and 2018 were due to outbreaks which occurred in Sabah with 235 and 163 cases reported in the respective years. It is an acute enteric infection caused by the ingestion of the bacterium *Vibrio cholerae* O1 or O139. The disease is transmitted through the faecal-oral route and through ingestion of contaminated water or food. It can cause severe diarrhoea with or without vomiting. Death can occur in a few hours due to dehydration, electrolyte imbalance, acidosis, shock, hypoglycaemia and renal failure.

Cholera is treated with oral rehydration salts, intravenous fluids and other supportive measures. Appropriate antibiotics may be given to severe cases to diminish the duration of diarrhoea, reduce the volume of rehydration fluids needed and shorten the duration of *Vibrio* excretion. It is controlled from spreading by public health measures and prevented by good hygiene, good sanitation and clean water supply.

The use of vaccines has now been advocated as an additional measure of lowering the risk of acquiring and transmitting the infection. However, the vaccine should not be used to treat a cholera infection. No adverse effects have been noted in pregnant women or the immunocompromised who were given the vaccine. However, it should only be used if the benefit outweighs the risk.

Cholera

Vaccines

1. Dukoral® (WC/rBS)

It is an oral vaccine consisting of killed whole-cell *V. cholerae* O1 with purified recombinant B subunit of cholera toxin (WC/rBS). The protection starts approximately 1 week after ingestion of the 2nd dose and gives a demonstrated protection of 85-90% at 6 months in all age groups, and of 62% at 1 year among adults.

2. Vaxchora, PaxVax, Redwood City, California

Live attenuated oral cholera vaccine (lyophilised CVD 103-HgR). It is approved in the USA only for use in travelers to cholera affected areas.

Vaccines Available in Malaysia

1. Dukoral® (Cholera and ETEC-diarrhoea)

- AJ Biologics Sdn Bhd/ Valneva, Sweden

- The vaccine is supplied in 3mL single-dose vials, each with a sachet of sodium bicarbonate buffer.
- Each dose of the vaccine should be administered in 150mL of water (75mL for children aged 2-6 years) mixed with the buffer.
- It cannot be administered to children aged <2 years.
- 2 doses are given orally with a minimum of 1 week and a maximum of 6 weeks apart.
- Vaccinees must be informed of the necessity to fast for 2 hours before and 1 hour after ingesting the dose.
- The reconstituted vaccine should be drunk within 2 hours.

Table 2.1
Characteristics of Cholera Vaccine Dukoral®

Characteristics of Dukoral® Vaccine	
Protection against *V. cholerae* O1	> 50% for 2 years
Exclusion criteria	Children <2 years old
Presentation	Oral suspension (vaccine) and effervescent granules (buffer)
Shelf-life	3 years
Storage	Cold chain (2-8°C)
Stability at ambient temperature	1 month at 37°C
Administration course	2 doses; 1 to 6 weeks apart
Amount of drinking water needed/ dose	Adults and children < 6 years old: 150ml Children 2-6 years old : 75ml

Adverse Effects

The most frequently reported adverse effects include gastrointestinal symptoms such as stomach pain, diarrhoea, nausea & vomiting. Other adverse effects such as headache, dizziness, fever, rash, itching, runny nose & cough have been reported.

Target Groups in Malaysia

- Travelers to areas in which there is a recognised risk of exposure to cholera. All travelers to cholera-affected areas should follow safe food and water precautions and proper sanitation and personal hygiene measures as primary strategies to prevent cholera.
- The course of vaccination should be completed at least one week before travel.
- During humanitarian crises with high risk of cholera, and during cholera outbreaks.

Cholera

Note:

- *The vaccine is not routinely recommended for travelers who are not visiting areas of active cholera transmission*.*
- **An area of active cholera transmission is defined as a province, state, or other administrative subdivision within a country with endemic or epidemic cholera caused by toxigenic V. cholerae O1 and includes areas with cholera activity within the last year that are prone to recurrence of cholera epidemics; it does not include areas where only rare imported or sporadic cases have been reported.*

Implications for Healthcare Workers (HCWs)

There is currently no recommendation for HCWs. Cholera vaccines may be employed as part of comprehensive control strategies in areas where the disease is endemic as well as to prevent and respond to cholera outbreaks.

Evidence for Effectiveness

- Both available formulations of the vaccines were effective in inducing a vibriocidal antibody response
- For recipients ages 5 to 15, the cholera vaccine was 52% effective in protecting against all cholera and 71% effective in protecting against **severe** episodes. For adults, the vaccine protective efficacy was 59% against all cholera episodes.

References

1. Ali, M., Nelson, A. R., Lopez, A.L, Sack, D. A. (2015). Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis, 9, e0003832 https://doi.org/10.1371/journal.pntd.0003832
2. Centers for Disease Control and Prevention (CDC). (2016). Department of Health and Human services. Advisory Committee on Immunization Practices. Summary Report. https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-2016-06.pdf
3. Centers for Diseases Control and Prevention (CDC). (2017). Recommendations of the Advisory Committee on Immunization Practices for Use of Cholera Vaccine. MMWR (66)18: 482-485. https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-2016-02.pdf
4. Malaysian National Centre of Adverse Drug Reactions database. https://npra.gov.my/
5. Ministry of Health of Malaysia (MOH). (2011-2019). Health facts: Incidence rate and mortality rate of communicable diseases. https://www.moh.gov.my/index.php/pages/view/58
6. Ministry of Health of Malaysia (MOH). (2016 &2019). Health Indicators: Indicators for Monitoring and Evaluation of Strategy Health for All. https://www.moh.gov.my/index.php/pages/view/58
7. Summary of WHO Position Paper. (2019). Immunisation of Healthcare workers. https://www.who.int/immunization/policy/Immunization_routine_table4.pdf
8. World Health Organization (WHO). (2005). Cholera. WHO position paper. Weekly Epidemiol Rec 81: 297-308. http://www.who.int/wer
9. World Health Organization. (2010). Cholera vaccines. WHO position paper. Weekly Epidemiol Rec 85: 117-128. http://www.who.int/wer

Diphtheria

Introduction

Diphtheria is an acute, communicable respiratory infection caused by *Corynebacterium diphtheriae*. The causative organism produces a toxin that results in local tissue destruction and produces membranous inflammation of the upper respiratory tract. The organism itself is rarely invasive, but a potent exotoxin produced by some strains (toxigenic strains) causes tissue damage through local and systemic actions. The toxin may then undergo haematogenous dissemination resulting in myocarditis and neuritis. Pharyngeal diphtheria, the commonest form of the disease can cause acute severe respiratory obstruction.

The disease is spread by transmission of respiratory tract droplet or by direct contact with skin lesions or articles soiled by infected persons. Humans are the only known reservoir of *Corynebacterium diphtheriae* and the disease is usually spread by close personal contact with a case or carrier. Carriers are important in disease transmission as natural or vaccine induced immunity does not prevent carriage.

In Malaysia, the incidence of the disease has declined dramatically with the introduction of routine childhood immunisation and improved living standards. The incidence rate of diphtheria has been sustained to less than 1 per 100,000 population for the past 20 years. There were no cases reported in 2011 and 2012. However, the disease started to re-emerge in 2013 and has shown a dramatic increase in 2016 and 2017 with 31 and 32 cases reported in the respective years. In 2018, the number of cases reported was 18 with an incidence rate of 0.05 per 100,000 population.

Although childhood vaccination coverage is important to produce herd immunity, it is known that immunity acquired from childhood vaccination wanes in the absence of boosters later in life, and older adults might not be adequately protected. It has been shown that only 60% of the overall population sample had immunity to diphtheria (defined as an anti-diphtheria toxoid concentration of >0.1 IU/mL). This immunity declined progressively with increasing age from 91% at age 6–11 years and 80% among adolescents aged 12–19 years, to approximately 30% among those aged 60–69 years.

Vaccines

- This is a toxoid-derived vaccine that is adsorbed onto an adjuvant (aluminium salt, usually aluminium phosphate) to increase its immunogenicity.
- Diphtheria toxoid is only available as a component of combination vaccines. The diphtheria vaccine is present in combination with tetanus toxoid (DT, Td) or with both tetanus toxoid and pertussis (DTaP/Tdap).
- Other combinations available include DTaP-HepB-Hib-IPV and DTaP-IPV/Hib which are mainly used in childhood immunisation.

Note:

Upper-case letters in the above abbreviations denote full-strength doses of diphtheria (D) and tetanus (T) toxoids and pertussis (P) vaccine. Lower-case "d" and "p" denote reduced doses of diphtheria and pertussis used in the adolescent/adult formulations. The "a" in DTaP and Tdap stands for "acellular", meaning that the pertussis component contains only a part of the pertussis organism.

Vaccines Available in Malaysia

1. Adacel® (Tdap; tetanus-diphtheria-acellular pertussis)
Sanofi Pasteur (M) Sdn Bhd/Sanofi Pasteur Limited, Canada
2. Adacel® Polio (Tdap -IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)
Sanofi Aventis (M) Sdn Bhd/Sanofi Pasteur, France
3. Boostrix® (Tdap; tetanus-diphtheria-acellular pertussis)
GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

Diphtheria

4. Boostrix-Polio®
(Tdap-IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)

GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd / GlaxoSmithKline Biologicals S.A.,Belgium

5. Infanrix Hexa®
(DTaP; diphtheria-tetanus-acellular pertussis inactivated polio-Hib-Hep B)

GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

6. Infanrix-IPV+Hib®
(DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio-Hib)

GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

7. Infanrix-IPV®
(DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio)

GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

8. Adsorbed DT (DT; diphtheria- tetanus)

Propharm (M) Sdn Bhd/FT Bio Farma, Indonesia

9. DTP (DTP; diphtheria-tetanus-acellular pertussis)

Propharm (M) Sdn Bhd/FT Bio Farma, Indonesia

10. Pentaxim®
(DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio/Hib)

Sanofi-Aventis (M) Sdn Bhd/Sanofi Pasteur, France

11. Hexaxim®
(DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio-Hib-Hep B)

Sanofi-Aventis (M) Sdn Bhd/Sanofi Pasteur, France

12. SII Diphtheria and Tetanus Vaccine Adsorbed (Paediatric) - 10 and 20 doses (DT; diphtheria-tetanus)

SM Pharmaceuticals Sdn Bhd/Serum Institute of India

13. SII Diphtheria, Tetanus and Pertussis Vaccine Adsorbed- 10 and 20 doses (DTaP; diphtheria-tetanus-acellular pertussis)

SM Pharmaceuticals Sdn Bhd/Serum Institute of India

Mode of Administration

The dose is 0.5mL given by intramuscular (IM) injection.

Co-administration with Other Vaccines

Several vaccines can be given together as long as there are no contraindications for individual agents. There are no contraindications to simultaneous administration of live attenuated vaccines with inactivated or toxoid vaccines. Do not mix Tdap or Td vaccines with other vaccines in the same syringe unless approved for mixing by the manufacturer.

Contraindications and Adverse Effects

The only absolute contraindication to diphtheria containing vaccine is anaphylaxis reaction after the previous dose or to any component of the vaccine.

Adverse effects reported include pain, tenderness, localised erythema and oedema at the injection site. Fever, headache, lethargy and myalgia are rare.

To date the most frequently reported adverse events for diphtheria containing vaccines in children received by the National Pharmaceutical Regulatory Agency (NPRA) include injection site reactions such as injection site erythema, fever and rash. Cases of febrile seizures and convulsions have also been reported in children.

Diphtheria

Target Groups in Malaysia

- All adults lacking a completed primary series of diphtheria and tetanus toxoids should complete the series with Tdap/Td.
- All adults for whom 10 years or more have elapsed since completion of their primary series, or since their last booster dose, should receive a dose of Tdap. Thereafter, a booster dose of Td should be administered every 10 years. There is no need to repeat doses if the schedule for the primary series or booster doses is delayed. For those in contact with small children, Tdap as the 1st dose may be more appropriate to prevent the transmission of pertussis. Subsequent booster doses of Td every 10 years can then be given.
- Patients who have recovered from diphtheria should complete the full immunisation schedule as the disease does not confer immunity.
- All household and other close contacts who have received less than 3 doses of diphtheria toxoid or whose vaccination status is unknown, should receive an immediate dose of a diphtheria toxoid containing preparation and should complete the primary series according to schedule. Close contacts who have completed a primary series of 3 doses or more and, who have not been vaccinated with diphtheria toxoid within the previous 5 years, should receive a booster dose of a diphtheria toxoid-containing preparation appropriate for their age.

Implications for Healthcare Workers (HCWs)

Regardless of age, all HCWs should receive a single dose of Tdap, as soon as feasible, if they have not previously received it. Tdap can be administered regardless of interval since the last tetanus or diphtheria containing vaccine. Td boosters are advocated every 10 years thereafter.

Evidence for Effectiveness

Complete immunisation induces protective levels of diphtheria antitoxin which lasts throughout childhood. However, by middle age, at least 50% of persons not vaccinated since childhood have antitoxin levels <0.1IU/ml. A level >0.1IU/ml is required to provide definite and prolonged protection. The administration of a single dose of toxoid in previously immunised adults would be able to induce protective levels within 6 weeks.

Recommendations for Vaccination for Pertussis, Tetanus, and Diphtheria

- **Primary vaccination in adults:** Three doses of vaccine are required with an interval of 4-6 weeks between the 1st and 2nd doses, and 6-12 months between the 2nd and 3rd doses. Tdap can be used for the 1st dose with Td vaccine for the subsequent doses.

- **Booster vaccination:** Persons aged ≥19 years who previously have not received a dose of Tdap should receive a single dose of Tdap. To ensure continued protection against tetanus and diphtheria, booster doses of Td should be administered every 10 years throughout life.

- Do **NOT** administer DTaP to adolescents and adults as the higher doses of the diphtheria and pertussis components may result in greater adverse effects.

References

1. Centers for Disease Control and Prevention (CDC). (2011). Recommendations of the Advisory Committee on Immunisation Practices (ACIP). Immunisation of Health-Care Personnel, MMWR, 60(RR07), 1-45. https://www.cdc.gov/mmwr/pdf/rr/rr6007.pdf
2. Centers for Disease Control and Prevention (CDC). (2018). Recommendations of the Advisory Committee on Immunization Practices. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: MMWR, 67(2), 1-44 https://www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm
3. Malaysian National Centre of Adverse Drug Reactions database. https://npra.gov.my/
4. Marlovit, S., Stocker,R., Efstratiou, A., et al. (2000). Effect on diphtheria immunity of combined tetanus and diphtheria booster vaccination in adults. Eur J Clin Microbiol Infect Dis, 19, 506-13
5. McQuillan, G.M., Kruszon-Moran, D., Deforest, A., Chu, S.Y., Wharton, M. (2002). Serologic immunity to diphtheria and tetanus in the United States. Ann Intern Med, 136, 660-6
6. Ministry of Health of Malaysia (MOH). (2011-2019). Health facts: Incidence rate and mortality rate of communicable diseases. https://www.moh.gov.my/index.php/pages/view/58
7. Mohd Khalid, M.K.N., Ahmad, N., Fen Hii, S. Y., Abd Wahab, M.A., Hashim, R., Liow, Y.L. (2018). Molecular characterization of Corynebacterium diphtheriae isolates in Malaysia between 1981 and 2016. Journal of Medical Microbiology, 68, 105-110. https://doi.org/10.1099/jmm.0.000881
8. Ministry of Health Malaysia. (2019). National Pharmaceutical Control Bureau (NPCB). Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah
9. Sutter, R.W., Hardy, I.R., Kozlova, I.A., et al. (2000). Immunogenicity of tetanus-diphtheria toxoids (Td) among Ukrainian adults: Implications for diphtheria control in the Newly Independent States of the former Soviet Union. J Infect Dis, 181 Suppl 1, S197-202 60(RR07): 1-45

Introduction

Tetanus is caused by *Clostridium tetani* which produces a potent toxin that has two components, i.e., tetanospasmin (alpha-neurotoxin) and tetanolysin (alpha-haemolysin). The organisms usually gain entry through open wounds and lacerations or via penetrating injuries. Neonatal tetanus is due to infection of the baby's umbilical stump. Tetanus is not transmitted from person to person.

Tetanospasmin is mainly responsible for the features of tetanus which manifests as rigidity and painful spasms of skeletal muscles. The muscle stiffness usually involves the jaw (lockjaw) and neck and then becomes generalised. The disease is often fatal and death results from respiratory failure, hypotension or cardiac arrhythmia.

The case-fatality ratio for tetanus is highest in infants and the elderly and is approximately 10%-20% even in modern health care facilities. The risk for both tetanus disease and mortality was higher among persons aged ≥65 years than in persons aged <65 years. Tetanus occurs almost exclusively among persons who are unvaccinated or inadequately vaccinated or in those whose vaccination histories are unknown.

Due to widespread immunisation, tetanus is now a rare disease in Malaysia. In 2018, the incidence rate of neonatal tetanus and other tetanus was 0.08 and 0.09 per 100,000 population respectively.

As tetanus is associated with apparently minor or trivial injury, especially in the elderly, active immunisation is thus important for its prevention.

Vaccines

- This is a toxoid-derived vaccine that is adsorbed onto an adjuvant (aluminium salt, usually aluminium phosphate) to increase its immunogenicity. Tetanus toxoid is available as a combination with

diphtheria toxoid (DT, Td), or with both diphtheria toxoid and pertussis (DTaP/Tdap).

- DT is given to children younger than 7 years of age while Tdap is used in adolescents and adults.
- Other combinations available include DTaP-HepB-Hib-IPV and DTaP-Hib-IPV which are mainly used in childhood immunisation.

Note:

Upper-case letters in the above abbreviations denote full-strength doses of diphtheria (D) and tetanus (T) toxoids and pertussis (P) vaccine. Lower-case "d" and "p" denote reduced doses of diphtheria and pertussis used in the adolescent/adult formulations. The "a" in DTaP and Tdap stands for "acellular", meaning that the pertussis component contains only a part of the pertussis organism.

Vaccines Available in Malaysia

A. Tetanus® toxoid

1. **TT Vaccine®** (Adsorbed tetanus vaccine)
   Propharm (M) Sdn Bhd/PT Bio Farma, Indonesia
2. **Tetanus Toxoid Vaccine®** (Adsorbed tetanus vaccine)
   SM Pharmaceuticals Sdn Bhd/Serum Institute of India, India

B. Combination vaccines

1. **Adacel®** (Tdap; tetanus-diphtheria-acellular pertussis)
   Sanofi Aventis (M) Sdn Bhd /Sanofi Pasteur Limited, Canada
2. **Adacel® Polio** (Tdap -IPV; tetanus-diphtheria-acellular pertussis inactivated polio)
   Sanofi Aventis (M) Sdn Bhd/Sanofi Pasteur, France

B. Combination vaccines

3. **Boostrix**® (Tdap; tetanus-diphtheria-acellular pertussis)
   GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
4. **Boostrix-Polio**® (Tdap-IPV; diphtheria-tetanus-acellular pertussis-inactivated polio)
   GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
5. **Infanrix Hexa**® (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio-Hib-Hep B)
   GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
6. **Infanrix-IPV+Hib**® (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio-Hib)
   GlaxoSmithKline Pharmaceutical Sdn Bhd / GlaxoSmithKline Biologicals S.A., Belgium
7. **Infanrix-IPV** (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio)
   GlaxoSmithKline Pharmaceutical Sdn Bhd / GlaxoSmithKline Biologicals S.A., Belgium
8. **Adsorbed DT**® (DT; diphtheria- tetanus)
   Propharm (M) Sdn Bhd/ FT Bio Farma, Indonesia
9. **DTP**® (DTP; tetanus-diphtheria-acellular pertussis)
   Propharm (M) Sdn Bhd/ FT Bio Farma, Indonesia
10. **Pentaxim**® (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio/Hib)
    Sanofi-Aventis (M) Sdn Bhd/ Sanofi Pasteur, France
11. **Hexaxim**® (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio-Hib-Hep B)
    Sanofi-Aventis (M) Sdn Bhd/ Sanofi Pasteur, France

12. **SII Diphtheria and Tetanus Vaccine Adsorbed®** (Paediatric) -10 and 20 doses) (DT; diphtheria-tetanus)
    SM Pharmaceuticals Sdn Bhd/ Serum Institute of India
13. **SII Diphtheria, Tetanus and Pertussis Vaccine Adsorbed®** - (10 and 20 doses) (DTaP; diphtheria-tetanus-acellular pertussis)
    SM Pharmaceuticals Sdn Bhd/ Serum Institute of India

C. Tetanus Immune Globulin (TIG)

1. **Sero-Tet®** (Human tetanus immune globulin)
   Propharm (M) Sdn Bhd /Green Cross Corporation, South Korea
2. **Igantet®** (Human antitetanus Ig)
   Grifols (M) Sdn Bhd /Instituto Grifols S.A., Spain

Mode of Administration

The dose of all tetanus-containing vaccines is 0.5mL, to be given by intramuscular (IM) injection.

Co-administration with Other Vaccines

Several vaccines can be given together as long as there are no contraindications for individual agents. There are no contraindications to simultaneous administration of live attenuated vaccines with inactivated or toxoid vaccines. Do not mix tetanus toxoid with other vaccines in the same syringe, unless approved for mixing by manufacturer.

Contraindications and Adverse Effects

The only absolute contraindication to tetanus containing vaccines is anaphylaxis reaction after the previous dose, or to any component of the vaccine.

Common adverse effects include pain, tenderness, localised erythema and discomfort at the injection site. Uncommon general adverse effects following Td vaccination include headache, lethargy, malaise, myalgia and fever. Anaphylaxis, urticaria and peripheral neuropathy occur very rarely.

The adverse reactions to a single dose of Tdap are similar in adults and adolescents, whether administered shortly (18 months) or at a longer interval after a previous dose of a vaccine containing tetanus/diphtheria toxoids. Thus, frequent administration of tetanus toxoid does not increase the risk of developing injection site reaction as had been perceived previously.

To date, the most frequently reported adverse events for tetanus toxoid vaccines received by National Adverse Drug Reactions Monitoring Centre, NPCB include local site reactions such as injection site pain and swelling, fever and rash.

Target Groups in Malaysia

- All adults (parents, siblings, grandparents, child-care providers and healthcare personnel) who have or anticipate having close contact with an infant aged <12 months should receive a single dose of Tdap to protect against pertussis if they have not received Tdap previously.

- Adults who have never been vaccinated should be given the complete 3-dose primary series which comprises a 1st dose of Tdap followed by 2 doses of Td. Adults whose vaccination status is unknown should also be given the complete 3-dose primary series.

- All adults who have not completed the primary series of diphtheria and tetanus toxoids should complete the primary series, one of which should include the Tdap.

- All adults who have not had a booster dose in 10 years or more should receive a booster dose of Tdap vaccine. Thereafter, a booster dose should be administered every 10 years.

- All pregnant women at each pregnancy, irrespective of the patient's prior history of receiving Tdap. Optimal timing is in the 3rd trimester, between 27 and 36 weeks gestation, to maximise the maternal antibody response and passive antibody transfer to the infant.
- Pregnant women with unknown or incomplete tetanus vaccination should receive 3 vaccinations containing tetanus and reduced diphtheria toxoids.
- Patients who have recovered from tetanus should complete the full immunisation schedule as the disease does not confer immunity.
- Patients with tetanus prone wounds. These wounds are other than clean, minor cuts. The types of wounds that are more likely to favour the growth of *C. tetani* are compound fractures, bite wounds, wounds containing foreign bodies (wood splinters or rose thorns), wounds with extensive tissue damage and wounds obviously contaminated with soil. Post exposure prophylaxis and wound management is given below.

Post-exposure Prophylaxis and Treatment

For wound management, the need for active immunisation, with or without passive immunisation, depends on the condition of the wound and the patient's vaccination history (refer to Table 3.1).

Implications for Healthcare Workers (HCWs)

A dose of Tdap is recommended to be given as soon as feasible to all healthcare workers who have not received Tdap previously. Td boosters are advocated every 10 years thereafter.

Evidence for Effectiveness

Tetanus vaccination stimulates the production of antitoxin and protects

against the toxin produced by *Clostridium tetani* in contaminated wounds; however, it does not prevent the growth of the organism.

Complete immunisation (3 primary doses and 2 booster doses) induces protective levels of antitoxin throughout childhood and into adulthood. However, by middle age, about 50% of vaccinated persons will have waned immunity. A single dose of tetanus toxoid produces a rapid anamnestic response in such persons.

Table 3.1 Guide to Tetanus Prophylaxis in Wound Management

History of tetanus vaccination	Time since last dose	Type of Wound	Tdap, DTaP combinations, DT, Tdap (as appropriate)	Tetanus immunoglobulin (TIG)
>3 doses	<5 yrs	Minor clean wounds	No	No
		All other wounds†	No	No#
>3 doses	5-10 yrs	Minor clean wounds	No	No
		All other wounds†	Yes	No#
>3 doses	>10 yrs	Minor clean wounds	Yes	No
		All other wounds†	Yes	No#
<3 doses or uncertain§		Minor clean wounds	Yes	No
		All other wounds†	Yes	Yes

*The recommended dose for TIG is 250IU, given by IM injection, as soon as practicable after the injury. If more than 24 hours have elapsed, 500IU should be given. Because of its viscosity, TIG should be given to adults using a 21 gauge needle. For children, it can be given slowly using a 23 gauge needle.

† All wounds other than minor clean wounds should be considered 'tetanus-prone'.

Individuals with humoral immune deficiency (including HIV-infected persons who have immunodeficiency) should be given TIG if they have received a tetanus-prone injury, regardless of the time since their last dose of tetanus-containing vaccine.

§ Persons who have no documented history of a primary vaccination course (3 doses) with a tetanus toxoid-containing vaccine should receive all missing doses and must receive TIG

Tetanus

Recommendations for Vaccination for Pertussis, Tetanus, and Diphtheria

- **Primary vaccination in adults:** Three doses of vaccine are required with an interval of 4-6 weeks between the 1st and 2nd doses, and 6-12 months between the 2nd and 3rd doses. Tdap can be used for the 1st dose with Td vaccine for the subsequent doses.

- **Booster vaccination:** Persons aged ≥19 years who previously have not received a dose of Tdap should receive a single dose of Tdap. To ensure continued protection against tetanus and diphtheria, booster doses of Td should be administered every 10 years throughout life.

- Do **NOT** administer DTaP to adolescent and adults as the higher doses of the diphtheria and pertussis components may result in greater adverse effects.

References

1. Centers for Disease Control and Prevention (CDC). (2018). Recommendations of Advisory Committee on Immunization Practices. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States. MMWR, 67(2), 1-44 https://www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm
2. Centers for Disease Control and Prevention (CDC). (2008). Recommendations for Postexposure Interventions to Prevent Infection with Hepatitis B Virus, Hepatitis C Virus, or Human Immunodeficiency Virus, and Tetanus in Persons Wounded During Bombings and Other Mass-Casualty Events in United States. MMWR, 57(RR06), 1-19 https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5706a1.htm
3. Centers for Disease Control and Prevention (CDC). (2011). Advisory Committee on Immunisation Practices (ACIP). Immunisation of Health-Care Personnel. MMWR, 2011, 60(RR07), 1-45. https://www.cdc.gov/mmwr/pdf/rr/rr6007.pdf
4. Centers for Disease Control and Prevention (CDC). (2012). Advisory Committee on Immunisation Practices (ACIP). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women. MMWR, 62(07), 131-135. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6207a4.htm
5. Halperin, S. A., Sweet, L., Baxendale, D., et al. (2006). How soon after a prior tetanus-diphtheria vaccination can one give adult formulation tetanus-diphtheria-acellular pertussis vaccine? Pediatr Infect Dis J, 25, 195-200
6. Malaysian National Centre of Adverse Drug Reactions database. https://npra.gov.my/
7. Marlovits, S., Stocker, R., Efstratiou, A., et al. (2000). Effect on diphtheria immunity of combined tetanus and diphtheria booster vaccination in adults. Eur J Clin Microbiol Infect Dis 19, 506-13
8. McQuillan, G. M., Kruszon-Moran, D., Deforest, A., Chu, S. Y, Wharton, M. Serologic immunity to diphtheria and tetanus in the United States. Ann Intern Med, 136, 660-6
9. Ministry of Health of Malaysia (MOH). (2019). Health facts: Incidence rate and mortality rate of communicable diseases. https://www.moh.gov.my/index.php/pages/view/58
10. Ministry of Health Malaysia. (2019). National Pharmaceutical Regulatory Agency (NPRA). Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah.
11. Rushdy, A. A., White, J. M., Ramsay M. E., Crowcroft , N. S. Tetanus in England and Wales, 1984– 2000. Epidemiol Infect, 130, 71-7
12. Talbot, E. A., Brown, K. H., Kirkland, K. B., et al. (2010). The safety of immunising with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine, 28, 8001-7

Introduction

Pertussis also known as whooping cough, is an upper respiratory tract infection caused by *Bordetella pertussis*. Transmission is via direct contact with respiratory secretion or by aerosolised droplets from the infected persons. Its classical presentation is characterised by paroxysmal cough with inspiratory whoop. However, adolescents and adults who are infected experience a milder form of the symptoms due to the presence of varying degrees of immunity acquired from childhood vaccination or past infection. Adults can suffer from a chronic cough for weeks or months and often are misdiagnosed for bronchitis or other respiratory infections.

In recent years, there has been an epidemiological shift towards higher incidences of pertussis among adolescents and adults due to waning immunity. Epidemiologic data indicate that adults who are family members, particularly parents are the most important source of pertussis to susceptible children. In more than 50% of primary cases, parents are the presumed source of infection.

In Malaysia, the incidence of pertussis was less than 0.1 per 100,000 population in the 1990s and early 2000s. In the mid-2000s, a higher incidence in pertussis was attributed to an actual increase in the burden of disease which were also reflected in the improvement in the detection of the organism by molecular diagnosis, increased health care personnel and public awareness of pertussis, and better reporting of cases. In recent years (2014-2017), the cases continued to escalate with incidence rates ranged between 0.94-3.08 per 100,000 population and mortality rates between 0.01-0.04 per 100,000 population.

The last pertussis booster vaccine under the Malaysian National Immunisation Programme is given at 18 months of age. It is therefore expected that immunity would have diminished during adolescence; hence adults are once again susceptible to pertussis and may become potential reservoirs.

Pertussis

Vaccines

- Pertussis vaccine is available as an acellular formulation in combination with diphtheria, tetanus and other antigens.
- Tdap is the adult formulation of tetanus, diphtheria and acellular pertussis containing vaccine. Tdap contains substantially lesser amounts of diphtheria toxoid and pertussis antigens than the child formulation (DTaP).
- Other combinations available include DTaP-HepB-Hib-IPV and DTaP-Hib-IPV which are mainly used in childhood immunisation.
- There are a number of acellular pertussis containing vaccines that contain two or more purified components of *Bordetella pertussis* depending on the manufacturer. The components are pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN) and fimbrial (FIM) antigens.

Note:
Upper-case letters in the above abbreviations denote full-strength doses tetanus (T) toxoids. Lower-case "d" and "p" denote reduced doses of diphtheria and pertussis. The "a" in Tdap stands for "acellular", meaning that the pertussis component contains only a part of the pertussis organism.

Vaccines Available in Malaysia

1. Adacel® (Tdap; tetanus-diphtheria-acellular pertussis)
Sanofi Pasteur (M) Sdn Bhd/Sanofi Pasteur Limited, Canada
2. Adacel® Polio (Tdap-IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)
Sanofi Aventis (M) Sdn Bhd/Sanofi Pasteur, France

3. Boostrix® (Tdap; tetanus-diphtheria-acellular pertussis)
GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
4. Boostrix-Polio® (Tdap-IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)
GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
5. Infanrix Hexa® (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio-Hib-Hep B)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
6. Infanrix-IPV+Hib® (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio-Hib)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
7. Infanrix-IPV® (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
8. DTP (DTP; tetanus-diphtheria-acellular pertussis)
Propharm (M) Sdn Bhd/FT Bio Farma, Indonesia
9. Pentaxim® (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio/Hib)
Sanofi-Aventis (M) Sdn Bhd/Sanofi Pasteur, France
10. Hexaxim® (DTaP; diphtheria-tetanus-acellular pertussis-inactivated polio-Hib-Hep B)
Sanofi-Aventis (M) Sdn Bhd/Sanofi Pasteur, France

11. SII Diphtheria and Tetanus Vaccine Adsorbed (Paediatric) - 10 and 20 doses) (TD; tetanus-diphtheria)
SM Pharmaceuticals Sdn Bhd/Serum Institute of India
12. SII Diphtheria, Tetanus and Pertussis Vaccine Adsorbed- 10 and 20 doses) (DTaP; diphtheria-tetanus-acellular pertussis)
SM Pharmaceuticals Sdn Bhd/Serum Institute of India

Mode of Administration

The dose of pertussis-containing vaccines is 0.5mL to be given by IM injection.

Co-administration with Other Vaccines

Several vaccines can be given together as long as there are no contraindications for individual agents. There are no contraindications to simultaneous administration of live attenuated vaccines with inactivated or toxoid vaccines. Do not mix tetanus toxoid with other vaccines in the same syringe unless approved for mixing by manufacturer.

Contraindications and Adverse Effects

- The only absolute contraindications to acellular pertussis containing vaccines are anaphylaxis, following a previous dose and anaphylaxis following any vaccine component.
- The reduced antigen content of the adult formulations of Tdap vaccines are safe and well tolerated in adults. The incidence of fever is low. Booster doses of Tdap given within 10 years are also safe and well tolerated in adults and limb swelling reactions following booster doses rarely occur.

- Adverse effects include pain, tenderness, localised erythema and oedema at the injection site have been reported. Fever, headache, lethargy and myalgia are rare.

- To date, the most frequently reported adverse events of pertussis containing vaccines in children received by the National Adverse Drug Reactions Monitoring Centre (NPRA) include injection site reactions such as injection site erythema, fever and rash. Cases of febrile seizure and convulsions had also been reported in children.

Target Groups in Malaysia

- Adults aged ≥ 19 years who have not been immunised with Tdap or for whom vaccine status is unknown.

- Pregnant women. The optimal timing for the vaccine administration is between 27 and 36 weeks gestation to maximise the maternal antibody response and passive antibody transfer to the infant. Maternal anti-pertussis antibodies are short-lived. Thus, Tdap vaccination in one pregnancy will not provide sufficiently high levels of antibodies to protect the newborn during subsequent pregnancies. Thus, it is recommended Tdap be given at **every pregnancy** regardless of previous receipt of Tdap.

- Adolescents and adults (e.g., parents, siblings, grandparents) who have or anticipate having close contact with an infant aged <12 months.

- Staff working in early childhood education and care (kindergarten and nursery).

Implications for Healthcare Workers (HCWs)

- A dose of Tdap is recommended to be given to all HCWs, as soon as feasible, if they have not received Tdap previously. Vaccinating HCWs with Tdap will protect them against pertussis and is expected to reduce transmission to patients and other HCWs. Tdap boosters are recommended every 10 years thereafter.

Additional Doses of Tdap for the General Population

- Tdap is licensed for use as a single dose for active booster immunisation; Boostrix® and Adacel® are approved for use in persons aged 4 years and above.
- Tdap is not licensed for multiple administrations nor is it recommended for multiple administrations, with the exception of the recommendation that pregnant women receive a dose of Tdap during each pregnancy.
- If a dose of Tdap is administered to a person who has previously received Tdap, this dose should count as the next booster dose of tetanus toxoid–containing vaccine.

Evidence of Effectiveness

An anamnestic response can be induced with the administration of a booster dose of Tdap, which is the adult formulation. A randomised trial in adults reported a point estimate of 92% efficacy against culture/nucleic acid test-positive disease within 2.5 years of vaccination, with a 3 component monovalent pertussis vaccine. A long term follow-up of adults vaccinated with Tdap vaccine has shown a rapid decline in levels of pertussis antibodies, within the first 2 years after vaccination, with a continued steady decline up to 10 years after vaccination, although antibody levels remained above baseline. The rate of decline in clinical protection is unknown, but

protection against clinical disease, is likely to persist for up to 10 years and is immunogenic in the elderly.

Recommendations for Vaccination for Pertussis, Tetanus, and Diphtheria

- **Primary vaccination in adults:** Three doses of vaccine are required with an interval of 4-6 weeks between the 1st and 2nd doses, and 6-12 months between the 2nd and 3rd doses. Tdap can be used for the 1st dose with Td vaccine for the subsequent doses.

- **Booster vaccination:** Persons aged ≥19 years who previously have not received a dose of Tdap should receive a single dose of Tdap. To ensure continued protection against tetanus and diphtheria, booster doses of Td should be administered every 10 years throughout life.

- Do **NOT** administer DTaP to adolescent and adults as the higher doses of the diphtheria and pertussis components may result in greater adverse effects.

References

1. Bisgard, K. M., Pascual, F. B., Ehresmann, K. R., et al. (2004). Infant pertussis: who was the source? Pediatr Infect Dis J, 23, 985-9
2. Booy, R., Van der Meeren, O., Ng, S. P., et al. (2010). A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix™) is immunogenic and well tolerated in adults. Vaccine, 29, 45-50
3. Centers for Disease Control and Prevention (CDC) (2018). Advisory Committee on Immunization Practices (ACIP). Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States. MMWR, 67(2), 1-44. https://www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm
4. Centers for Disease Control and Prevention (CDC). (2011). Advisory Committee on Immunisation Practices (ACIP). Immunisation of Health-Care Personnel. MMWR, 60(RR07), 1-45. https://www.cdc.gov/mmwr/pdf/rr/rr6007.pdf
5. Güriş, D., Strebel P.M., Bardenheier, B., et al. (1999). Changing epidemiology of pertussis in the United States: Increasing reported incidence among adolescents and adults, 1990–1996. Clin Infect Dis, 28, 1230-7
6. Healy, C. M., Rench, M. A., Baker, C. J. (2013). Importance of timing of maternal Tdap immunization and protection of young infants. Clin Infect Dis, 56, 539–44
7. Malaysian National Centre of Adverse Drug Reactions database. https://npra.gov.my
8. Ministry of Health Malaysia. (2019). National Pharmaceutical Regulatory Agency (NPRA). Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah
9. Ministry of Health of Malaysia (MOH). (2014-2018). Health facts: Incidence rate and mortality rate of communicable diseases. https://www.moh.gov.my/index.php/pages/view/58
10. Van Damme, P., McIntyre, P., Grimprel, E., et al. (2011). Immunogenicity of the reduced-antigen-content Tdap vaccine (Boostrix®) in adults 55 years of age and over: A sub-analysis of four trials. Vaccine, 29, 5932-9
11. Ward, J. I., Cherry, J.D., Chang, S. J, et al. (2005). Efficacy of an acellular pertussis vaccine among adolescents and adults. New Engl J Med, 353, 1555-63
12. Wendelboe, A.M., Njamkepo, E., Bourillon, A., et al. (2007). Transmission of Bordetella pertussis to young infants. Pediatr Infect Dis J, 26, 293-9

Haemophilus Influenzae

Introduction

Haemophilus influenzae is a gram-negative coccobacillus that exists as encapsulated and non-encapsulated strains. Based on the chemical composition of the polysaccharide capsule, the encapsulated strains may be further classified into 6 serotypes (a, b, c, d, e, and f). Non-encapsulated strains are non-typeable. Both encapsulated and non-encapsulated strains are pathogenic to humans.

Among the strains, *H. influenzae* type b (Hib) is the most virulent strain and responsible for more than 95% of invasive diseases in children. The gram negative bacteria first colonises the host's nasopharynx, and subsequently either (a) invades the blood stream which results in bacteraemia and secondary spread can lead to meningitis, epiglottitis, pneumonia, arthritis, osteomyelitis and cellulitis [which are collectively known as invasive disease], or (b) spreads contiguously to adjacent sinuses or middle ear and results in sinusitis or otitis media, respectively.

Prior to the widespread use of Hib vaccine in resource-limited countries, Hib was estimated to have resulted in 371,000 deaths and >8 million serious infections in children aged <5 years old in 2000 alone. The number of deaths caused by Hib had reduced significantly to 203,000 in children aged <5 years old in 2008; the year when the total number of WHO member states that had introduced Hib vaccine into their national immunisation programmes rose to 136 from 62 in 2000.

The other encapsulated strains of *H. influenzae* occasionally cause invasive disease similar to that of Hib while the non-encapsulated strains cause mucosal infections, including otitis media, conjunctivitis, sinusitis, bronchitis and pneumonia. These strains rarely cause invasive disease in children. In adults, non-encapsulated strains account for nearly 50% of invasive infections.

Vaccines

The Hib vaccine is derived from the polyribosylribitol phosphate (PRP) capsule of the bacteria. The PRP capsule is a key virulence determinant of the organism. It enables the bacterium to evade phagocytosis of leucocytes and therefore facilitates systemic dissemination through the blood stream. The specific antibody to PRP is the primary contributor to immunity, and increasing levels of antibody are associated with decreasing risk of invasive Hib disease. Like other bacteria-derived polysaccharides, the immune response to PRP is a T-cell independent antigen response, where B lymphocytes provide the primary response without a contribution from T-helper cells. As a result, the antibody response to pure polysaccharide antigen is poor in children less than 18 months. In order to improve the immunogenicity of PRP, the polysaccharide antigen is conjugated with a T-cell dependent protein antigen, like diphtheria toxoid – hence the term, conjugate vaccine.

Vaccines Available in Malaysia

1. Hiberix® (*H. infleunzae* type b)
GlaxoSmithKline Pharmaceutical (M) Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

Mode of Administration

Hib vaccines are administered by intramuscular injection into the anterolateral aspect of the deltoid or thigh. It should not be administered intravenously, intradermally, or subcutaneously.

In children, primary immunisation comprises 3 doses that are given during the first 6 months of age. In Malaysia, under the National Immunisation Programme (NIP), the immunisation is given at 2, 3 and 5 months. A booster dose is given at 18 months.

In adults the dosing regimen would depend on the circumstances for vaccination.

Co-administration with Other Vaccines

Hib vaccine can be co-administered with other injectable vaccines, but should not be mixed with any other vaccine in the same syringe or vial. Hib vaccine should be given in separate syringes and at different injection sites.

Contraindications and Adverse Effects

- The vaccine should not be administered to individuals with:
  - » Confirmed anaphylactic reaction to Hib-containing vaccine.
  - » Confirmed anaphylactic reaction to neomycin, streptomycin or polymyxin B, as they may be present in small amounts.
  - » Acute illness with systemic upset and fever.
  - » Evolving or undiagnosed, deteriorating neurological abnormalities.
- Severe adverse events following administration of Hib vaccine are uncommon, making it one of the safest vaccines currently available. In a study of >4,000 infants, there were no differences in the type and frequency of severe adverse events occurring among those receiving Hib conjugate vaccine and those receiving a placebo. Mild adverse effects are reaction at the site of injection (10%) and fever (2%).
- To date, the most frequently reported adverse events for Hib vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) include local site reactions such as injection site inflammation, swelling, fever and rash.

Target Groups in Malaysia

Hib vaccine is primarily a vaccine for children. However, Hib vaccination should be given to the following adults:

- Anatomical or functional asplenia: For those who have not received or completed Hib immunisation in childhood – 1 dose 2 weeks before elective splenectomy or as soon as possible after an emergency splenectomy.

- Recipients of bone marrow transplants – 3 doses at 12, 14 and 24 months after successful transplantation regardless of Hib vaccination history.

Evidence for Effectiveness

The introduction of Hib vaccine has considerably reduced the reported incidents of Hib diseases in all settings regardless of their level of socioeconomic status and development. In addition the nasopharyngeal colonisation rate of Hib in the population has also declined with the widespread use of Hib vaccine, which has contributed to a reduction in disease incidence of Hib through the establishment of herd immunity. Countries which have introduced mass immunisation have witnessed near elimination of invasive Hib infections. There is however less evidence of efficacy in adults.

References

1. Greenberg, D. P., Doemland, M., Bettinger, J. A., Scheifele, D. W., Halperin, S. A., Waters, V., Kandola, K. (2009). Epidemiology of Pertussis and *Haemophilus influenzae* type b Disease in Canada With Exclusive Use of a Diphtheria-Tetanus-Acellular Pertussis-Inactivated Poliovirus-*Haemophilus influenzae* type b Pediatric Combination Vaccine and an Adolescent-Adult Tetanus-Diphtheria-Acellular Pertussis Vaccine. The Pediatric Infectious Disease Journal, 28(6), 521-528. doi:10.1097/inf.0b013e318199d2fc
2. Haemophilus b Conjugate Vaccines for Prevention of *Haemophilus influenzae* Type b Disease Among Infants and Children Two Months of Age and Older Recommendations of the ACIP. (1991). PsycEXTRA Dataset. doi:10.1037/e546452006-001
3. *Haemophilus influenzae* type b (Hib). (2014, January 24). Retrieved from https://www.who.int/immunization/diseases/hib/en/
4. The Malaysian National Centre for Adverse Drug Reactions Database. Accessed: October 10, 2019.
5. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Received September 5, 2019.
6. Observed Rate of Vaccine Reactions Global Vaccine Safety (2002). Retrieved December 1, 2013, from https://www.who.int/vaccine_safety/initiative/tools/Influenza_Vaccine_rates_information_sheet.pdf?ua=1
7. WHO. (2013, October 21). *Haemophilus influenzae* type b (Hib) Vaccination WHO position paper: July 2013 Recommendations. Retrieved from https://www.sciencedirect.com/science/article/pii/S0264410X13014217?via=ihub

Hepatitis A

Introduction

Hepatitis A is an acute infectious disease of the liver caused by hepatitis A virus (HAV). HAV is classified in the genus enterovirus of the family Picornaviridae, based on its biophysical and biochemical characteristics.

HAV is transmitted by the faecal-oral route. Person-to-person spread is the most common method of transmission in developed countries. Infections occur readily under condition of poor sanitation, hygiene and overcrowding. Subclinical infection is common in children and severity tends to increase with age. Occasional cases of fulminant hepatitis may occur but there is no chronicity.

Hepatitis A occurs endemically in all parts of the world with frequent reports of minor and major outbreaks. The exact incidence is difficult to estimate because of the high proportions of subclinical infection and infections without jaundice, differences in surveillance systems and differing patterns of disease. The degree of under-reporting is very high.

Hepatitis A has been a notifiable disease in Malaysia since 1988. The overall incidence of hepatitis A has decreased significantly from 11.65 (1988), 9.16 (1991), 4.72 (1997), 0.41 (2013) to 0.30 (2018) per 100,000 population. On the other hand, the seroprevalance rate has also decreased from 67% (1986) to 54.9% (1993) and 48.4% (2000).

In terms of age-related seroprevalence of HAV infection, Malaysia portrays a pattern typical of declining endemicity (i.e. from intermediate to low endemicity). The proportion of seroconverted children and adolescents has decreased in line with socioeconomic development. However, a relatively high seroprevalence still occurs in older adults (76.1% among those aged 41-60 years) although this is expected to decline as younger adults replace the current cohort.

There is an obvious shift of the seroprevalence curve in Malaysia to the right and downwards from 1986 to year 2000, similar to the one shown by developed countries like Singapore and the United States.

Vaccines

All available inactivated hepatitis A vaccines contain HAV antigen. Most will have aluminium hydroxide or aluminium hydroxyphosphate as adjuvant. They are available in paediatric and adult formulations.

Vaccines Available in Malaysia

1. Avaxim® (Hepatitis A)
Sanofi Aventis (M) Sdn Bhd/Sanofi Pasteur, France
2. Havrix® (Hepatitis A)
GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
3. Twinrix® (Hepatitis A and B)
GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

Mode of Administration

- The primary vaccination consists of 1 single dose of vaccine followed by a booster injection preferably 6-12 months after the first vaccination. The booster dose is extended up to 36 months for some vaccines.
- For combined hepatitis A and hepatitis B vaccine, a 3-dose series is required at 0, 1, 6 months; minimum intervals: 4 weeks between first and second doses, 5 months between second and third doses.
- The vaccine should be given intramuscularly in the deltoid region. In exceptional circumstances (in patients with thrombocytopenia or in patients at risk of haemorrhage), the vaccine may be injected by the subcutaneous route; however, this may be associated with a higher risk of local reaction including injection site nodule.

- The vaccine should not be administered into the gluteal muscles of the buttocks (due to the presence of varying amounts of adipose tissue) or intradermally since these modes of administration may induce a lesser degree of immune response.

Co-administration with Other Vaccines

- Combination inactivated hepatitis A and hepatitis B vaccine (Twinrix®) is also available. In some countries, combination vaccines for the prevention of hepatitis A and typhoid fever are available, incorporating *Salmonella typhi Vi* capsular polysaccharide antigen packaged in a dual-chamber bypass syringe (Vivaxim®).

Contraindications and Adverse Effects

- Immunisation should be postponed in individuals suffering from severe febrile illness. Since it is an inactivated vaccine, the risks of adverse effects to the foetus are likely to be negligible but it should NOT be given in pregnancy unless there is a definite risk of infection.

- Adverse effects are usually mild and confined to the first few days after immunisation. The most common reactions are mild transient soreness, erythema and induration at the injection site. General symptoms such as fever, malaise, fatigue, headache, nausea and loss of appetite are also reported, though less frequently.

- To date, the most frequently reported adverse events for hepatitis A vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) are local site reactions such as injection site pain, swelling and rash. Systemic reactions such as pruritus and urticaria have also been reported.

Target Groups in Malaysia

- Travelers to countries where hepatitis A endemicity is high.
- Patients with chronic liver disease.
- Haemophiliacs.
- Occupational exposure: healthcare workers, food handlers and laboratory personnel.
- Men who have sex with men.
- Injection drug users.
- Individuals at risk during outbreaks.

Implications for Healthcare Workers (HCWs)

Outbreaks of hepatitis A among hospital staff occur occasionally, usually in association with an unsuspected index patient who is faecally incontinent. In most outbreaks, nurses accounted for the majority of personnel infected. However, HCWs were not found to have an increased prevalence of anti-HAV compared to control populations in serologic surveys.

Evidence for Effectiveness

- The vaccines are highly immunogenic in persons aged ≥18 years when administered according to the recommended schedules. Protective antibody levels developed in 94-100% of adults, 1 month after the 1st dose. After the 2nd dose, all persons had protective levels of antibody, with high geometric mean antibody concentrations (GMCs).

- Protective levels of anti-HAV were still observed in 99% of 549 children evaluated 5-6 years after receiving the vaccine. Estimates of antibody persistence indicate that protective levels of anti-HAV could be present for ≥20 years. Whether other mechanisms (cellular memory) also contribute to long-term protection is unknown.

References

1. Doebbeling, B. N., Li, N., & Wenzel, R. P. (1993). An outbreak of hepatitis A among health care workers: risk factors for transmission. American Journal of Public Health, 83(12),1679-1684.
2. Favero, M. S., Maynard, J. E., Leger, R. T., Graham, D. R. & Dixon, R. E. (1979). Guidelines for the care of patients hospitalised with viral hepatitis. Annals of Internal Medicine, 91,872-876.
3. Gibas, A., Blewett, D. R., Schoeneld, D. A. & Dienstag, J. L. (1992). Prevalence and incidence of viral hepatitis in health workers in the prehepatitis B vaccination era. American Journal of Epidemiology, 136,603-610.
4. The Malaysian National Centre of Adverse Drug Reactions Database [Accessed: 10 October 2019]
5. McMahon, B. J., Williams, J., Bulkow, L., Snowball, M., Wainwright, R., Kennedy, M. & Krause, D. (1995). Immunogenicity of an inactivated hepatitis A vaccine in Alaska Native children and native and non-native adults. Journal of Infectious Diseases, 171,676-679.
6. Ministry of Health (2020, October 15) Malaysia Health Facts 2019. https://www.moh.gov.my/moh/resources/Penerbitan/Penerbitan%20Utama/HEALTH%20FACTS/Health%20Facts%202019_Booklet.pdf
7. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Received on 5 September 2019.
8. Wiedermann, G., Kindi, M. & Ambrosch, F. (1998). Estimated persistence of anti-HAV antibodies after single dose and booster hepatitis A vaccination (0–6 schedule). Acta Tropica 69,12-125.
9. Wiens, B., Bohidar, N., Pigeon, J. G., Egan, J., Hurni, W., Brown, L, Kuter, B. J. & Nalin D. R. (1996).Duration of protection from clinical hepatitis A disease after vaccination with VAQTA. Journalof Medical Virology,49,235–241.

Introduction

Hepatitis B is a common form of hepatitis which can be transmitted parenterally, through sexual contact and from mother to infant. It is an important cause of acute and chronic infection of the liver. More than a third of the world's population is infected with the hepatitis B virus (HBV), and WHO estimates that it results in 1 – 2 million deaths annually.

The virus persists in 5-10% of immunocompetent adults and in as many as 90% of infants infected perinatally. Persistent carriage of HBV is defined by the presence of hepatitis B surface antigen (HBsAg) in the serum for more than 6 months. It occurs in more than 350 million individuals worldwide. Long-term continuing virus replication may lead to chronic liver disease, cirrhosis and hepatocellular carcinoma. Primary liver cancer is one of the ten most common cancers worldwide and about 80% of these are ascribed to persistent infection with HBV.

Malaysia was an intermediate endemicity country with HBsAg prevalence of 5 – 7% before nationwide HBV vaccination for neonates was introduced in 1989 as part of the Expanded Programme for Immunisation. The programme was successful as the prevalence of chronic HBV infection among those born in 1999 and 2000 is 0.3% as compared to 1.7% among those born in 1986 to 1988. Overall, there is serological evidence that the universal infant HBV immunisation programme in Malaysia has been effective in reducing the rate of chronic HBV infection in individuals up to about 24 years of age. In 2018, the incidence rate and mortality rate is 14.52 and 0.21 per 100,000 population.

Vaccines

- Hepatitis B vaccine contains HBsAg adsorbed on aluminum hydroxide adjuvant. HBsAg is prepared from yeast cells using recombinant DNA technology.

Hepatitis B

Vaccines Available in Malaysia

1. Euvax-B® (Hepatitis B)

Sanofi Aventis (M) Sdn Bhd/LG Chem Ltd, South Korea

2. Engerix-B® (Hepatitis B)

GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

3. Hepavax-Gene TF® (Hepatitis B)

Propharm (M) Sdn Bhd/Berna Biotech Korea Corporation, South Korea

4. Twinrix® (Hepatitis A and B)

GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd / GlaxoSmithKline Biologicals S.A., Belgium

5. SII Hepatitis-B Vaccine®

SM Pharmaceuticals (M) Sdn Bhd/Serum Institute of India, India

6. HBvaxPRO®

Merck Sharp & Dohme (M) Sdn Bhd/Merck Sharp & Dohme Corp, USA

7. Hepabig Injection® (Hepatitis B immune globulin)

Propharm (M) Sdn Bhd/Green Cross Corporation, South Korea

Mode of Administration

- The basic immunisation regimen consists of 3 doses of vaccine, with the 1st dose at the elected date, the 2nd dose 1 month later and the 3rd dose at 6 months after the 1st dose. This schedule gives optimal protection by the 7th month and produces high antibody titres.

- An accelerated schedule – with immunisation at 0, 1 and 2 months
  - » will confer protection more quickly and is expected to provide better patient compliance. With this schedule, the 4th dose should be administered at 12 months, as titres after the 3rd dose are lower than those obtained after the 0, 1 and 6 months schedule.

- If an even more rapid induction of protection due to exceptional circumstances is required (such as travelling to areas of high endemicity within 1 month), a schedule of 3 doses given at 0, 7 and 21 days may be used for subjects aged 20 years or older. When this schedule is applied, a 4th dose is recommended 12 months after the 1st dose.

- In subjects aged 11-15 years, the vaccine may be administered according to a 0, 6 months schedule. However, protection against hepatitis B infections may not be obtained until after the 2nd dose. Therefore, this schedule should be used only when there is a low risk of hepatitis B infection during the vaccination course and when completion of the 2-dose vaccination course can be assured. If both conditions cannot be assured (for instance, patients undergoing haemodialysis, travelers to endemic regions and close contacts of infected subjects), the 3-dose or the accelerated schedule should be used.

- Heplisav-B® (Dynavax) is a new single-antigen recombinant hepatitis B vaccine with a novel adjuvant. It is recommended for adults ≥ 18 years old and administered in two doses given ≥ 4 weeks apart. Pregnant women should not receive Heplisav-B® as safety data on administration during pregnancy is not available.

- WHO does not recommend booster vaccination, as it has been shown that the 3-dose series of hepatitis B immunisation protects for as long as 15 years and that a protective anamnestic response occurs after exposure to HBV, even if protective antibodies have been undetectable by laboratory tests over time.

- The vaccine should be given intramuscularly. It may be administered subcutaneously in patients with thrombocytopenia or bleeding disorders. It should not be administered in the buttock or intradermally, since this may result in a lower immune response.

Co-administration with Other Vaccines

- A combination inactivated hepatitis A and hepatitis B vaccine (Twinrix®) is also available.

Contraindications and Adverse Effects

- Hepatitis B vaccine is generally well tolerated. The most commonly reported adverse reactions are soreness, erythema and swelling at the injection site. These reactions are mild and usually subside within 2 days after vaccination. General symptoms such as fever, headache, nausea, dizziness, and fatigue rarely occur.

- To date, the most frequently reported adverse events for Hepatitis B vaccines received by the National Adverse Drug Reactions Monitoring Centre (NPRA) are local site reactions such as injection site swelling rash, fever, and pruritus.

Target Groups in Malaysia

- Adults who are at a higher risk of hepatitis B (see below) and:
  - » Have not been previously immunised should receive the full course of vaccination.
  - » Have not completed their primary vaccination should be given the missing doses.

- The following adults at higher risk of hepatitis B and should be screened for their immune status regardless of whether they have had previous vaccination:
  - » Parenteral drug abusers.
  - » Close family contact of a case or those chronically infected.
  - » Haemophiliacs.
  - » Patients with chronic renal failure.
  - » Patients with chronic liver disease.
  - » Healthcare workers.
  - » Staff and residents of residential accommodation for mentally handicapped.
  - » Travelers to areas of high endemicity.
  - » Patients attending STD and HIV clinics.
  - » Men who have sex with men.
  - » Those with multiple sex partners.

Implications for Healthcare Workers (HCWs)

- HBV infection is a well-recognised occupational risk for healthcare workers. The risk of HBV infection is primarily related to the degree of contact with blood in the workplace, particularly with percutaneous exposure. HBV infections that occur in HCWs with no history of exposure might have resulted from direct or indirect blood or body fluid exposures that inoculated HBV into the mucosal surfaces or cutaneous scratches and other lesions.

- Vaccination against HBV and demonstration of immunisation before employment are strongly recommended. A study in Kuala Lumpur in 2005 revealed that only 58.4% of HCWs had completed their hepatitis B vaccination. Thus, hospital managements must make serious efforts to improve the coverage.

- Pre-vaccination serology screening for previous infection is not indicated for HCWs unless the hospitals or healthcare institutions consider screening cost-effective.

  » After completion of the 3-dose vaccination series, anti-HBs testing should be tested in 1–2 months. If anti-HBs is less than 10mIU/mL (or negative), the HCW is unprotected from HBV infection and should complete a 2nd 3-dose vaccine series or be evaluated to determine if they are HBsAg-positive. Revaccinated persons should be retested at the completion of the 2nd vaccine series. Primary non-responders to vaccination who are HBsAg-negative should be considered susceptible to HBV infection and should be counselled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known or probable parenteral exposure to HBsAg-positive blood. Persons who prove to be HBsAg-positive should be counselled accordingly.

- For post-exposure prophylaxis, please refer to the section on Passive Immunisation (pg 176).

Evidence for Effectiveness

- Anti-HBs is the only easily measurable correlate of vaccine-induced protection using serologic assays. Anti-HBs concentration of 10mIU/mL or more, measured 1-3 months after the administration of the last dose of the primary vaccination series, is considered a reliable marker of protection against infection. This is even if anti-HBs concentrations may decline over time to less than 10mIU/mL (as it also involves the induction of memory B and T cells).

- In immunocompromised patients who have ongoing exposure to HBV, annual anti-HBs testing is recommended and booster doses are required to maintain anti-HBs concentrations of 10mIU or higher.

- Observational studies have shown that a primary series of hepatitis B vaccine can prevent infection for more than 20 years, despite decrease or loss of vaccine-induced anti-HBs over time.

References

1. Hesham, R., Zamberi, S., Tajunisah, M. E., Ariza, A. & Ilina, I. (2005). Hepatitis B immunisation status among health care workers in two Kuala Lumpur hospitals. Medical Journal of Malaysia, 60(4):407-410.
2. Lauer, J. L., VanDrunen, N. A., Washburn, J. W. & Balfour, H. H. Jr. (1979). Transmission of hepatitis B virus in clinical laboratory areas. Journal of Infectious Disease. 140(4):513-516.
3. Lopez, C. G. (1985). Epidemiology of persistent hepatitis B virus infection. Malaysian Journal of Pathology, 7:7-10.
4. The Malaysian National Centre of Adverse Drug Reactions Database [Accessed: 10 October 2019]
5. MOH Malaysia. Hepatitis B Seroprevalence Study Among Children Year 3 and 4. 2009 (unpublished)
6. Ministry of Health (2020, October 15) Malaysia Health Facts 2019. https://www.moh.gov.my/moh/resources/Penerbitan/Penerbitan%20Utama/HEALTH%20FACTS/Health%20Facts%202019_Booklet.pdf
7. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Received on 5 September 2019.
8. Ng, K. P., Saw, T. L., Baki, A., Rozainah, K., Pang, K. W. & Ramanathan, M. (2005). Impact of Expanded Programme of Immunisation on hepatitis B infection in school children in Malaysia. Medical Microbiology and Immunology, 194:163-168.
9. Van Damme P, Ward J, Shouval D, Wiersma S, Zanetti A. Hepatitis B vaccines. Vaccines, Ed Plotkin S, Ed Orenstein W and Ed O t P. Elsevier, 2013. 205-234

Human Papillomavirus

Introduction

Human papillomaviruses (HPVs) are small, non-enveloped, double-stranded DNA viruses in the Papillomaviridae family. The genome is enclosed by an icosahedral capsid composed of major and minor structural proteins, L1 and L2 respectively. HPVs are highly tissue-specific and infect both cutaneous and mucosal epithelium. More than 200 HPV types have been identified and about 40 HPV types infect the anogenital tract. Some HPV types, including types 16, 18, 31, 33, 35, 45, 52 and 58, are 'high-risk', as they are causally associated with the development of cancer in humans. The International Agency for Research on Cancer defines 12 HPV types as 'high-risk': types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59. Other HPV types, including types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 73, 81 and 89, are classified as 'low-risk' and are predominantly associated with non-malignant lesions, such as genital warts. Infection with HPV is very common in both men and women, with initial infection related to the time of sexual debut.

HPV infection is often sub-clinical and transient, but low-risk HPV types may cause lesions that include cutaneous warts, genital warts and respiratory papillomatosis. The low-risk HPV types 6 and 11 cause 90% of anogenital warts and almost all recurrent respiratory papillomatosis. Anogenital HPV infection with low-risk types causes benign skin and mucosal tumours, including anogenital warts in both females and males (condylomata acuminata or venereal warts). In a systematic review of global estimates, the overall reported annual incidence of anogenital warts in both males and females, (including new and recurrent) ranged from 160 to 289 per 100 000. Prevalence ranged from 0.15% to 0.18% in the general population.

High-risk HPV types may cause dysplasias and cancers of the cervix, vulva, vagina, penis, anus, the oral cavity and oropharynx. Most genital HPV infections are self-limiting with complete recovery but in about 20% of infections, the virus persists. Persistent infections, within months or years, may progress towards premalignant glandular or squamous intra-epithelial lesions, classified histopathologically as cervical intra-epithelial neoplasia (CIN), and to HPV-associated cancers. CIN is further classified as: CIN 1: mild

dysplasia; CIN 2: moderate to marked dysplasia; and CIN 3: severe dysplasia to carcinoma-in-situ. Most CIN lesions regress spontaneously, though over a number of years, the lesions can slowly become cancerous.

HPV-16 and HPV-18 are the most frequent types worldwide, with HPV-16 the most common type in all regions. Worldwide, high risk HPV types 16 and 18 cause about 70% of cases of cervical cancers. HPV-16 and 18 are associated with 85% of HPV-related head and neck cancers and 87% of anal cancers. HPV types 16, 18, 45, 31, 33, 52, and 58 account for approximately 90% of the squamous cell carcinomas which are positive for HPV DNA. It was estimated that 630 000 new HPV-related cancers occurred in females in 2012, of which 528 000 (84%) were cervical cancer and 266,000 female deaths, accounting for 8% of all female cancer deaths that year. The majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers. Most of these occur in females who are not screened or who do not receive early treatment. In Malaysia, statistics prior to 2007 and the National Cancer Registry data for 2007-2011 reported cervical cancer as the third most common cancer among women in Malaysia after breast and colorectal cancers.

Persons infected with one HPV type may be co-infected or subsequently infected with other types. HIV-positive men who have sex with men showed the highest HPV prevalence. Anal HPV infections are very common in men who have sex with men, and almost universal among people with HIV infection.

High risk HPV 16 and 18 which cause about 70% of cervical cancers, are covered by all three HPV vaccines. HPV 31, 33, 45 are the three high-risk types against which the bivalent vaccine (2vHPV) and quadrivalent vaccine (4vHPV) may afford cross-protection, which are associated with a further 13% of the cases. HPV 31, 33, 45, 52, 58 altogether (five high-risk types against which only 9vHPV affords direct protection) are associated with 18% of the cases, a further 5% compared with HPV 31, 33, 45.

Human Papillomavirus

WHO's Strategic Advisory Group of Experts (SAGE), on vaccines and immunisation recommended the use of HPV vaccine in November 2008. The updated complete position paper published in April 2018 incorporates recent developments concerning HPV vaccines, including the licensure of a nonavalent (9-valent) vaccine (9vHPV). New recommendations are proposed regarding vaccination strategies targeting girls only or both girls and boys, and vaccination of multiple birth cohorts. Vaccination of older adolescents and adults should be based on assessments of the potential benefits, based on their risks of HPV exposure.

Over 80 countries worldwide now have HPV vaccination programs. However, there are still barriers to HPV vaccine introduction, mostly in countries with the highest burden of cervical cancer and the greatest need for vaccination. The achievement of global target of 70% of countries introducing HPV vaccine by 2020 is thought to be unlikely.

HPV vaccination form part of a coordinated and comprehensive strategy to prevent cervical cancer and other diseases caused by HPV. Regular cervical screening, which detects histopathological changes, remains an important preventive measure against cervical diseases. Both are recommended. Vaccination protects against most, but not all, HPV types that cause cervical cancer as well as the broader spectrum of cancers and other HPV-diseases. There are also other infections and risk factors associated with cervical cancer. Likewise, cervical screening is not an alternative to HPV vaccination and is recommended for both vaccinated and unvaccinated women. The vaccines have no therapeutic effect on existing HPV-related conditions or diseases, but may prevent future dysplasia due to different HPV types targeted by the vaccine. The vaccine does not prevent other sexually transmitted infections. Therefore, all vaccinated individuals should continue to practice safe sex, abstinence or protective sexual behaviours, such as condom use.

Vaccines

Three highly efficacious HPV vaccines directed against high-risk HPV types are currently available and marketed in many countries worldwide. The vaccines are produced from non-infectious HPV virus-like particles (VLPs) developed through recombinant DNA technologies. The 4vHPV vaccine was first licensed in 2006, 2vHPV in 2007 and 9vHPV in 2014. Current evidence suggests that from the public health perspective, the three vaccines offer comparable immunogenicity, efficacy and effectiveness for the prevention of cervical cancer, which is mainly caused by HPV-16 and HPV-18. All three HPV vaccines have excellent safety profiles. The vaccines do not treat women with current HPV infection or related diseases. HPV vaccines are most efficacious in HPV-naive individuals, if administered before sexual debut. All three vaccines are registered for use in females, and the 4vHPV and 9vHPV vaccines are also registered for use in males.

1. Cervarix® – GlaxoSmithKline

- Bivalent HPV vaccine (2vHPV)
- Contains non-infectious major capsid (L1) protein of HPV types 16 and 18.
- Produced using a baculovirus expression system in *Trichoplusia ni* insect cell line.
- Volume of 0.5mL per dose, in vial or pre-filled syringe contains 20µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto a proprietary adjuvant system containing 500 µg of aluminum hydroxide and 50 µg of 3-O-desacyl-4-monophosphoryl lipid A (AS04).
- Indicated for use in females from the age of 10-45 years for the prevention of premalignant anogenital lesions affecting the cervix, vulva, vagina and anus, and cervical and anal cancers causally related to specific HPV types.

2. Gardasil® – Merck and Co., Inc

- Quadrivalent HPV vaccine (4vHPV).
- Contains non-infectious purified viral L1 capsid protein for HPV 6, 11, 16, and 18.
- The vaccine is produced using *Saccharomyces cerevisiae* (Baker's yeast), expressing L1 and includes amorphous aluminum hydroxyphosphate sulfate (AAHS) as adjuvant.
- Volume of 0.5mL per dose, in vial or pre-filled syringe contains 20µg HPV-6 L1 protein, 40µg HPV-11 L1 protein, 40µg HPV-16 L1 protein and 20µg HPV-18 L1 protein, adsorbed onto 225µg of aluminium hydroxyphosphate sulphate; 780µg L-histidine; 50µg polysorbate 80; 35µg sodium borate adjuvant. It may also contain yeast proteins.
- Gardasil is a vaccine indicated in girls and women 9-45 years of age for the prevention of cervical, vulvar, vaginal cancer; precancerous or dysplastic lesions and genital warts caused by HPV. Gardasil also provides protection in girls and women 9-26 years against anal cancer.
- Gardasil is indicated to prevent the following diseases:
  - » Cervical, vulvar and vaginal, and anal cancer caused by HPV types 16 and 18.
  - » Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
  - » Precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18: Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma in situ (AIS), cervical intraepithelial neoplasia (CIN) grade 1, vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3, vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3, anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

- Gardasil is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:
  - » Anal cancer caused by HPV types 16 and 18.
  - » Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
  - » Precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18: anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

3. Gardasil 9® – Merck and Co., Inc

- Nonavalent vaccine (9vHPV)
- Contains non-infectious purified major capsid (L1) protein for HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58.
- The vaccine is produced using *Saccharomyces cerevisiae* (Baker's yeast), expressing L1 and includes amorphous aluminum hydroxyphosphate sulfate (AAHS) as adjuvant.
- Volume of 0.5mL per dose, in vials or prefilled syringes. Contains 30 µg of HPV-6 L1 protein, 40 µg of HPV-11 L1 protein, 60 µg of HPV-16 L1 protein, 40 µg of HPV-18 L1 protein, 20 µg of HPV-31 L1 protein, 20 µg of HPV-33 L1 protein, 20 µg of HPV-45 L1 protein, 20 µg of HPV-52 L1 protein and 20 µg of HPV-58 L1 protein adsorbed on 500 µg AAHS.
- Gardasil 9 is a vaccine indicated in girls and women from 9 through 45 years of age for the prevention of cervical, vulvar, vaginal cancer, precancerous or dysplastic lesions and genital warts caused by HPV. Gardasil 9 also provides protection in girls and women 9- 26 years against anal cancer.

- Gardasil 9 is indicated to prevent the following diseases:
  - » Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
  - » Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
  - » Precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS), cervical intraepithelial neoplasia (CIN) grade 1, vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3, vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3, anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.
- Gardasil 9 is indicated in boys and men from 9 through 45 years of age for the prevention of anal cancer, anal precancerous or dysplastic lesions and external genital lesions (including genital warts) caused by HPV.
- Gardasil 9 is indicated to prevent the following diseases:
  - » Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
  - » Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
  - » Precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

Vaccines Available in Malaysia

1. Cervarix® (Human papillomavirus vaccine types 16 & 18)

GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

2. Gardasil® (Human papillomavirus vaccine types 6, 11, 16 & 18)
Merck Sharp & Dohme (M) Sdn Bhd/Merck Sharp & Dohme Corpe, USA
3. Gardasil 9® (Human papillomavirus vaccine types 6, 11, 16, 18, 31, 33, 45, 52 and 58)
Merck Sharp & Dohme (M) Sdn Bhd/Merck Sharp & Dohme B.V. Netherlands

Mode of Administration

The dose of HPV vaccines is 0.5mL, administered by intramuscular injections in the deltoid region, as a 2-dose schedule (0, 6-12 months). The 2nd dose should between 6 to 12 months after the first dose. In the year 2016, the two-dose schedule recommendation replaces the previous 3-dose schedule for persons starting HPV vaccination before the 15th birthday and for persons with certain immunocompromised conditions.

If the first dose of any HPV vaccine was given on or after the 15th birthday, vaccination should be completed according to a three-dose schedule. In a three-dose series, the second dose is recommended 1–2 months after the first dose, and the third dose is recommended six months after the first dose (0, 1–2, 6 month schedule).

If a vaccination schedule has been missed or interrupted, there is no need to repeat earlier doses. The number of recommended doses is based on age at administration of the first dose. The missed dose(s) should be given as soon as is practicable. The schedule should be completed for effective protection.

Co-administration with Other Vaccines

- HPV vaccines can be co-administered with other non-live and live vaccines because the HPV vaccines are not live vaccines. HPV vaccines can be administered with other vaccines at the same visit, using separate syringes and different injection sites.
- Co-administration of HPV vaccination with a booster dose of tetanus-diphtheria vaccination should be considered in vaccination programmes.

Contraindications and Adverse Effects

- The only absolute contraindications to HPV vaccines are those with:
  - » A history of immediate hypersensitivity or anaphylaxis following a previous dose of either HPV vaccine.
  - » A history of immediate hypersensitivity or anaphylaxis to any vaccine component.
    - ♦ The 2vHPV vaccine in prefilled syringes is contraindicated for persons with anaphylactic latex allergy.
    - ♦ The 4vHPV and 9vHPV vaccines are contraindicated for persons with a history of anaphylaxis to yeast.
    - ♦ Adverse events following HPV vaccination are generally non-serious and of short duration.
- HPV vaccines should not be given to:
  - » Those with moderate or severe acute illnesses. Wait until the illness improves before getting vaccinated.
  - » Pregnant women: data on the safety of HPV vaccination in pregnancy are limited, and HPV vaccination of pregnant women should be avoided. However, the vaccine has not been causally associated with adverse pregnancy outcomes or adverse effects on the developing foetus. If

pregnancy occurs after initiating the vaccination series, the remaining dose(s) should be delayed until after the pregnancy is completed. Termination of pregnancy is not indicated if vaccination was carried out inadvertently during pregnancy. Pregnancy testing is not indicated before giving the vaccine.

- HPV vaccines can be given to:
  - » Lactating women: breastfeeding is not a contraindication for HPV vaccination. Available evidence does not indicate an increased risk of adverse events linked to the vaccine in the mothers or their babies after administration of HPV vaccine to lactating women.
  - » Those with minor acute illnesses, such as diarrhoea or mild upper respiratory tract infections, with or without fever.
  - » Women who have had an equivocal or abnormal Pap test, a positive HPV test, or genital warts. These patients should be advised that the vaccine will not have any therapeutic effect on existing Pap test abnormalities, HPV infection or genital warts.
  - » Patients who are immunocompromised by infection, disease or medication. It should be noted that the immune response to vaccination and vaccine efficacy might be less in immunocompromised persons. HPV vaccine can be administered safely to immunocompromised and/or HIV-infected. HIV testing not a prerequisite for vaccination.
- Studies have shown HPV vaccines are safe and have no serious safety concerns. Studies showed that serious adverse effects following 2vHPV were similar in the vaccine and control groups. Post licensure data indicate that adverse events from 4vHPV are similar to those reported following other vaccines in adolescents.

- To date, the most frequently reported adverse events for HPV vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) are consistent with other studies which include injection site pain and erythema, swelling of the injection site, dizziness and headache.

- In 2013, The Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization (WHO), reviewed the safety of HPV vaccination. The Committee continued to be reassured by the safety profile of the available products. More than 170 million doses had been distributed worldwide at the time of review, and with more countries offering the vaccine through national immunisation programmes.

- Life-threatening allergic reactions from vaccines are very rare, which occur within a few minutes to a few hours after the vaccination. Syncope, brief fainting spells and related symptoms (such as jerking movements) can occur after any medical procedure, including vaccination. Recipients should be observed for 15 minutes after the vaccine is administered to avoid serious injury related to a syncopal episode.

Target Groups in Malaysia

- HPV immunisation programmes should initially prioritise high coverage in the primary target population of girls aged 9-14 years before potential exposure to HPV through sexual activity. Such programmes should be part of a coordinated strategy that includes education about risk behaviours for HPV infection and screening programmes for cervical cancer.

  The HPV vaccination programme was introduced in the Malaysian EPI in 2010, targeting girls aged 13 years. Vaccine is delivered through an on-going school based programme (Form 1, regardless of age) and to out-of-school girls aged 13 years.

- The HPV immunisation programme has been extended in 2012 to the catch-up group, targeting 18-year old girls. This was initiated by the Population and Family Development Board Malaysia (LPPKN) under the provision of Ministry of Women, Family and Community Development (KPWKM).

- For males aged 9-26 years: vaccination (4vHPV or 9vHPV vaccine series) is strongly recommended for men who have sex with men (MSM) and immunocompromised persons, including persons with HIV, who have not been previously vaccinated.

- For immunocompromised individuals: vaccination is recommended for adult men and women who are immunocompromised (such as due to HIV, medications or other conditions) if they were not fully vaccinated when they were younger, following risk assessment.

Recommendations

WHO recommends that routine HPV vaccination should be included in national immunisation programmes. For the prevention of cervical cancer, WHO's recommended primary target population is girls aged 9–14 years, prior to becoming sexually active. The initial vaccination of multiple cohorts of girls aged 9-14 is recommended when the vaccine is first introduced.

The current evidence supports the recommendation for a 2-dose schedule with adequate spacing between the first and second dose (0, 6-15 months) in females aged 9–14 years. Individuals ≥15 years and older should receive 3-dose schedule (0, 1–2, 6 months). Individuals known to be immunocompromised and/or HIV-infected (regardless of whether they are receiving ART) should also receive 3-dose schedule (0, 1–2, 6 months).

Interchangeability of the three vaccine types: currently, limited clinical data is available on safety, immunogenicity or efficacy of the vaccines when used interchangeably. Efforts should be made to administer the same vaccine for all doses. However, if the vaccine used for prior dose(s) is unknown or

unavailable, either of the HPV vaccines can be administered to complete the recommended schedule.

Where the course includes a combination of the 2 HPV vaccines, the person is considered to be fully immunised against HPV-16 and HPV-18 if a complete dose schedule of HPV vaccines have been given and the minimum interval requirements between the doses are adhered to. The need for a booster dose has not been established.

9vHPV may be used to continue or complete a vaccination series started with 4vHPV or 2vHPV. For persons who completed vaccination with 2vHPV or 4vHPV, there is no recommendation regarding additional vaccination with 9vHPV. The benefit of protection against the five additional types targeted by 9vHPV would be mostly limited to females for prevention of cervical cancers and precancers. Only a small percentage of HPV-associated cancers in males is due to the five additional types prevented by 9vHPV.

In June 2019, the Advisory Committee on Immunisation Practices (ACIP) approved two new recommendations for HPV vaccine:

1. "Catch-up" vaccination for males is recommended through age 26 years (previously through age 21 years). The catch-up recommendation for males is now the same with the recommendation for females.
2. Vaccination of persons 27 through 45 years of age based on "shared clinical decision-making" between the patient and the clinician. This means that the decision to vaccinate persons 27 through 45 years of age should be based on a discussion of benefits and risks between the patient and the clinician.

Vaccination of secondary target populations, such as females aged ≥15 years or males, is recommended only if this is feasible, affordable, cost-effective, and does not divert resources from vaccination of the primary target population or from effective cervical cancer screening programmes.

The choice of HPV vaccine should be based on assessment of locally relevant data, particularly the extent of HPV-associated public health burden (cervical cancer, other anogenital cancers, or anogenital warts), the population for

which the vaccines have been approved, and other characteristics, such as each vaccine features, price, supply, and other considerations.

For all three vaccines, the vaccination schedule depends on the age of the vaccine recipient.

- Females <15 years at the time of the first dose: a **2-dose schedule** with a 6-month interval between doses (0, 6-12 months) is recommended.
- Those aged ≥15 years at the time of the second dose are also adequately covered by 2 doses.
- Individuals ≥15 years at the time of first dose: a **3-dose schedule** (0, 1-2, 6 months).
- If the interval between doses is shorter than 5 months, then a third dose should be given at least 6 months after the first dose.
- An interval no greater than 12–15 months is suggested in order to complete the schedule promptly and before becoming sexually active.
- A **3-dose schedule** remains necessary for those known to be immunocompromised and/or HIV-infected (regardless of whether they are receiving antiretroviral therapy). It is not necessary to screen for HPV infection or HIV infection prior to HPV vaccination.
- HPV vaccines are not licenced for use in adults aged >45 years.
- For females:
  - » Girls aged 11-12 years should receive the 2vHPV, 4vHPV or 9vHPV vaccine series.
  - » Girls as young as 9 years can receive the vaccine.
  - » Females aged 13-26 years:
    - ♦ Who have not received the HPV vaccine in the past should be given a series of 2 or 3 doses.

- Who have not completed the full vaccine series should catch up on the missed doses.

- For males:
  - » Boys aged 11-12 years should receive the 4vHPV or 9vHPV vaccine series.
  - » Boys as young as 9 years can receive the vaccine.
  - » Males aged 13-26 years:
    - Who have not received the HPV vaccine in the past may still be given the series of 2 or 3 doses.
    - Who have not completed the full vaccine series may catch up on the missed doses.

Vaccination is strongly recommended for men who have sex with men (MSM) and immunocompromised persons, including persons with HIV, who have not been previously vaccinated.

- For immunocompromised individuals:

  Vaccination is recommended for adult men and women who are immunocompromised (such as due to HIV, medications or other conditions) if they were not fully vaccinated when they were younger. The decision should take into consideration their likelihood of previous exposure to HPV, future risks of exposure, the extent and duration of being immunocompromised. As HPV vaccines are not live viral vaccines, there are no specific safety concerns regarding administration to immunocompromised persons. It is not necessary to screen for HIV prior to HPV vaccination.

Implications for Healthcare Workers (HCWs)

- No special recommendations for health care workers, and they should follow the vaccine recommendations for adults based on age or other individual risk factors.

Evidence for Effectiveness

- Immunogenicity studies of both 2vHPV and 4vHPV vaccines have been conducted in girls aged 9-15 years. Very high antibody titres were demonstrated as compared to natural infection. Over 99% of the vaccinated girls in these studies developed antibodies after vaccination (high seropositivity rates). For 4vHPV vaccine, immunogenicity data in males also showed high seroconversion rates for all 4 HPV types.

- Both 2vHPV and 4vHPV vaccine were shown earlier as safe and provide high efficacy against HPV 16-and 18-related cervical pre-cancer lesions. The 4vHPV vaccine also has high efficacy against HPV 6- and HPV 11-related genital warts and anal cancers, as well as HPV 16- and 18-related vaginal and vulvar pre-cancer lesions. The consistency of several years of observations strongly suggests that similar high rates of protection can be expected against cervical cancer.

- The main efficacy study of 2vHPV vaccine was conducted in young women aged 15-25 years. The clinical trials demonstrated 93% vaccine efficacy in preventing cervical pre-cancers due to HPV 16 or 18, among the women who had not been previously exposed to a targeted HPV type. All studies of 2vHPV showed that more than 99% of females developed HPV-16 and HPV-18 antibody response 1 month after completing the 3-dose series.

- The main efficacy studies of the 4vHPV vaccine were conducted in young women and men, aged 16-26 years. Among persons not previously exposed to a targeted HPV type, the trials demonstrated nearly 100% vaccine efficacy in preventing cervical pre-cancers, vulvar and vaginal cancers, and genital warts caused by the vaccine types in women, as well as 90% vaccine efficacy in preventing genital warts and 75% vaccine efficacy in preventing anal pre-cancers in men. Clinical efficacy against infection and cervical, vaginal and vulvar lesions of any grade has been demonstrated. Among the HPV-naïve MSM, vaccine efficacy was 95% against intra-anal HPV infection and 75% against high-grade anal intraepithelial neoplasia from vaccine HPV types. Efficacy of 2vHPV in males has not been assessed.

- Evidence suggests that from the public health perspective, 2vHPV, 4vHPV and 9vHPV vaccines offer similar immunogenicity, efficacy and effectiveness for the prevention of cervical cancer (protection against selected cervical endpoints, such as cervical intraepithelial neoplasia grade 1 or more), which is mainly caused by HPV types 16 and 18. The serological response after vaccination is much stronger (1–4 logs higher) than the response after natural infection.

- Studies indicate that the vaccines are effective and suggest that vaccine protection is long-lasting. No evidence of waning protection after a 3-dose series of HPV vaccine has been found, after 10 years of follow-up from clinical trials. Data from long-term population-based follow-up studies indicate that protective antibody levels are predicted to remain well above the natural infection level for at least 20 years.

- For 9vHPV, a phase III efficacy trial comparing 9vHPV and 4vHPV among approximately 14,000 females aged 16 through 26 years showed non-inferior immunogenicity for the types shared by both vaccines and high efficacy for the five additional types. Non-inferior immunogenicity of 9vHPV compared to 4vHPV inferred efficacy for HPV 6, 11, 16 and 18. Other trials in the 9vHPV clinical development program included immunobridging studies that compared antibody responses across age groups and females and males and concomitant vaccination studies.

- After a 3-dose schedule, 2vHPV, 4vHPV and 9vHPV vaccines are highly immunogenic with the highest immune responses observed in girls aged 9–15 years. Antibody titres remain high for at least 10 years for 2vHPV with 100% seropositivity, for at least 9.9 years for 4vHPV, and for at least 5 years for 9vHPV in the currently available data.

- The 9vHPV is approved for males and females aged 9 through 45 years. The US FDA based this expanded approval on a study of 3,200 women aged 27 to 45 years. With a mean follow-up of 3.5 years, the vaccine had an effectiveness of 88% against prevention of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to nine HPV types covered by the

vaccine. The approval for men was based on inferences from the data in adult women, efficacy data from adolescents and men aged 16 to 26 years, as well as immunogenicity from 150 men aged 27 to 45 years who received a 3-dose regimen over 6 months.

- Based on immunogenicity data, a 2-dose schedule was approved for all 3 vaccines. Results of a systematic review indicate that immunogenicity of 2 vaccine doses (0, 6–12 months) in girls aged 9–14 years are non-inferior to 3 doses (0, 1–2, 6 months) in women aged 15–24 years. The outcomes included seroconversion, geometric mean titers (GMTs), or antibody avidity. Immunogenicity was found to be non-inferior with 2 doses, in persons aged 9 through 14 years compared with 3 doses in a group in which clinical efficacy was demonstrated (women aged 15-24 years), if the HPV vaccination series is initiated before the 15th birthday.

- Memory B cells elicited by the first vaccine dose require at least 4–6 months to mature and differentiate into high-affinity B cells. This implies that any vaccination schedule should include an interval of at least 4 months between the prime dose (first dose) and the prime-boost (last dose) to efficiently reactivate memory B cells and trigger their differentiation into antibody-secreting plasma cells. Two-dose schedules with shorter intervals might not allow this affinity maturation and could result in shorter duration of protection. Antibody kinetics similarity with 2-dose and 3-dose series implies that the duration of protection is expected to be long-lasting after a 2-dose series.

- Data on whether a 1-dose schedule confers adequate levels of protection are contradictory. A recent study found that the response to a single dose of 2vHPV conferred 100% seroprotection against HPV-16 and HPV-18 up to 4 years. In contrast, another study reported that after 5 years of follow-up, women who received a single dose of 4vHPV had a higher cumulative incidence (4.3%) of high-grade cytology, CIN, adenocarcinoma in situ, and invasive cervical cancer than women who received 2 doses (3.0% (P=0.04)).

- Studies on the immunogenicity of HPV vaccines in people who are immunocompromised and/or HIV-infected are limited. Data on the use

of HPV vaccines in a 3-dose schedule are reassuring in terms of safety in HIV-infected females, males, and children (aged 7–12 years). No data are available on use of the 2-dose schedule for the three vaccines in persons infected with HIV.

- Regarding the impact of vaccination programmes at the population level, there is evidence of a reduction in high grade cervical abnormalities among young women and vaccination significantly reduces the prevalence of high-risk HPV types among young women. Achieving high vaccination coverage in girls (>80%) reduces the risk of HPV infection for boys.

- HPV vaccination programmes are also effective in reducing the incidence of anogenital warts. The 4vHPV vaccine provides high-level protection against anogenital warts in men and women and anogenital precancerous lesions in susceptible men aged 16–26 years where introduction of this vaccine was followed by a rapid decline in the prevalence of genital warts.

- Comparisons of the cost-effectiveness of switching from 2vHPV or 4vHPV to 9vHPV vaccine in adolescent females are not yet established. The 9vHPV price per dose and the cross-protection provided by HPV vaccine types would influence the outcomes of cost-effectiveness analyses. Further data are also needed on the longer-term clinical effectiveness and the duration of protection, particularly for the 9vHPV vaccine.

References

1. Adult,& Schedule, I. (2020). Recommended Adult Immunization Schedule CDC 2019 guidelines. https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf
2. Aris, a. (2020). Cancer Registry Report. https://nci.moh.gov.my/index.php/ms/pengumuman/340-national-cancer-registry-report
3. Azizah Ab M, (2015). Summary of Malaysian National Cancer Registry Report 2007-2011. 1, 1–73. https://www.crc.gov.my/wpcontent/uploads/documents/report/MNCRRepor2007-2011.pdf
4. Center for Biologics Evaluation and Research, (2019) . Gardasil. U.S. Food and Drug Administration website: https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil
5. Center for Biologics Evaluation and Research, (2019). Gardasil 9 (human papillomavirus 9-valent vaccine,recombinant). Silver Spring, MD: US Department of Health and Human Services, Food andDrug Administration; 2018. https://www.fda.gov/media/90064/download
6. Center for Biologics Evaluation and Research. (2019). Cervarix. U.S. Food and Drug Administration website: https://www.fda.gov/vaccines-blood-biologics/vaccines/cervarix
7. Centers for Disease Control and Prevention (CDC). (2010). FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). MMWR. Morbidity and Mortality Weekly Report, 59(20), 626–629. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20508593
8. David, M.-P., Herck, V., Hardt, K., Tibaldi, F., Dubin, G., Descamps, D., & Damme, V. (2018). Long-term persistence of anti-HPV-16 and-18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: modeling of sustained antibody responses. GYNECOLOGIC ONCOLOGY, 115(3), S1–S6. Retrieved from https://biblio.ugent.be/publication/1246840
9. Descamps, D., Hardt, K., Spiessens, B., Izurieta, P., Verstraeten, T., Breuer, T., & Dubin, G. (2009). Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. Human vaccines, 5(5), 332–340. https://doi.org/10.4161/hv.5.5.7211
10. De Sanjose, S., Quint, W. G., Alemany, L., Geraets, D. T., Klaustermeier, J. E., Lloveras, B., Tous, S., Felix, A., Bravo, L. E., Shin, H. R, Kasamatsu, E., … Retrospective International Survey and HPV Time Trends Study Group (2010). Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. The Lancet. Oncology, 11(11), 1048–1056.
11. Gallagher K.E, N, H., Kabakama S, Mounier-Jack S, Griffiths U.K, Feletto M,… Watson-Jones, D. (2017). Lessons learnt from human papillomavirus (HPV) vaccination in 45 low- and middle-income countries. PLoS One, 12(6), e0177773–e0177773http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L616559985%0Ahttp://dx.doi.org/10.1371/journal.pone.0177773
12. Gerberding, J. L., Director Tanja Popovic, M., Stephens, J. W., Solomon, S. L., Bernhardt, J. M., Shaw, F. E., … John Ward, G. W. (2007). Morbidity and Mortality Weekly Report Quadrivalent Human Papillomavirus Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention Centers for Disease Control and Prevention Centers for Di. Mmwr, 5656. Retrieved from https://www.cdc.gov/mmwr/pdf/rr/rr5602.pdf
13. hpvcenter – International Human Papillomavirus Reference Center. (2020). Hpvcenter.se website: https://www.hpvcenter.se/
14. Iversen, O. E., Miranda, M. J., Ulied, A., Soerdal, T., Lazarus, E., Chokephaibulkit, K., Block, S. L., Skrivanek, A., Nur Azurah, A. G., Fong, S. M., Dvorak, V., Kim, K. H., Cestero, R. M., Berkovitch, M., Ceyhan, M., Ellison, M. C., Ritter, M. A., Yuan, S. S., DiNubile, M. J., Saah, A. J., … Luxembourg, A. (2016). Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women. JAMA, 316(22), 2411–2421. https://doi.org/10.1001/jama.2016.17615
15. Joura, E. A., Giuliano, A. R., Iversen, O. E., Bouchard, C., Mao, C., Mehlsen, J., Moreira, E. D., Jr, Ngan, Y., Petersen, L. K., Lazcano-Ponce, E., Pitisuttithum, P., Restrepo, J. A., Stuart, G., Woelber, L., Yang, Y. C., Cuzick, J., Garland, S. M., Huh, W., Kjaer, S. K., Bautista, O. M., … Broad Spectrum HPV Vaccine Study (2015). A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. The New England journal of medicine, 372(8), 711–723. https://doi.org/10.1056/NEJMoa1405044

16. Markowitz L.E, Dunne E.F, Saraiya M, Lawson H.W, Chesson H, Markowitz, L. E., … (ACIP), A. C. on I. P. (2007). Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. Recommendations and Reports : Morbidity and Mortality Weekly Report. Recommendations and Reports / Centers for Disease Control, 56(RR-2), 1–24. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=17380109
17. Meites, E., Szilagyi, P. G., Chesson, H. W., Unger, E. R., Romero, J. R., & Markowitz, L. E. (2019). Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR. Morbidity and Mortality Weekly Report, 68(32), 698–702. https://doi.org/10.15585/mmwr.mm6832a3
18. Meites, E., Kempe, A., Markowitz, L.E. (2016). Use of a 2-Dose Schedule for Human Papillomavirus Vaccination —Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2016;65:1405–1408. DOI: http://dx.doi.org/10.15585/mmwr.mm6549a5
19. Merck&Co. (2015). Package insert GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] Suspension for intramuscular injection. Merck&Co., 1–28. https://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf
20. Morbidity and Mortality Weekly Report (2012). Transmission of hepatitis C virus through transplanted organs and tissue - Kentucky and Massachusetts, 2011. American Journal of Transplantation, 12(3), 782–785. https://doi.org/10.1111/j.1600-6143.2012.04024.x
21. National Pharmaceutical Regulatory Agency (NPRA) - Home. (2020). https://npra.gov.my/index.php/en/
22. Noor, W. (2019). Retinoids: Updated measures for pregnancy prevention during retinoids use. https://npra.gov.my/index.php/en/health-professionals/recent-updates/414-english/safety-alerts-main/safety-alerts-2019/1527035-retinoids-updated-measures-for-pregnancy-prevention-during-retinoids-use.html
23. Paavonen, J., Naud, P., Salmerón, J., Wheeler, C. M., Chow, S. N., Apter, D., Kitchener, H., Castellsague, X., Teixeira, J. C., Skinner, S. R., Hedrick, J., … HPV PATRICIA Study Group (2009). Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet (London, England), 374(9686), 301–314. https://doi.org/10.1016/S0140-6736(09)61248-4
24. Petrosky, E., Bocchini, J. A., Jr, Hariri, S., Chesson, H., Curtis, C. R., Saraiya, M., Unger, E. R., Markowitz, L. E., & Centers for Disease Control and Prevention (CDC) (2015). Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. MMWR. Morbidity and mortality weekly report, 64(11), 300–304.
25. Safety of human papillomavirus vaccines. (2020). https://www.who.int/vaccine_safety/committee/topics/hpv/en/
26. SAGE meeting of October 2016. (2016). World Health Organization. https://www.who.int/immunization/sage/meetings/2016/october/presentations_background_docs/en/
27. Serrano, B., de Sanjosé, S., Tous, S., Quiros, B., Muñoz, N., Bosch, X., & Alemany, L. (2015). Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions. European journal of cancer (Oxford, England : 1990), 51(13), 1732–1741. https://doi.org/10.1016/j.ejca.2015.06.001
28. Weekly Epidemiological Record, 12 May 2017, vol. 92, 19 (pp. 241–268). (2017). World Health Organization. https://doi.org//entity/wer/2017/wer9219/en/index.html
29. WHO. (2017). HPV immunization schedules and strategies — Background paper for SAGE deliberations. 1–26. Retrieved from https://www.who.int/immunization/sage/meetings/2016/october/1_HPV_vaccine_background_document_27Sept2016.pdf?ua=1,%0Ahttp://www.who.int/immunization/sage/meetings/2016/october/1_HPV_vaccine_background_document_27Sept2016.pdf?ua=1,

Introduction

Influenza affects 5-15 % of the population annually. Influenza typically starts with fever, sore throat, headache, myalgia, chills, anorexia, and extreme fatigue followed by rhinorrhea and dry cough. The presence of cough and fever are the best predictors of influenza in adults and children during periods of influenza circulation. Rash has been described in influenza B. Uncomplicated influenza generally lasts 7 days. Infected persons are contagious one day before symptoms and up to 7 days after onset. In the elderly, fever may be absent while the presenting signs may include anorexia, lassitude or confusion. Asymptomatic influenza occurs in 30% of cases and they are infectious and transmit the infection.

The risk of developing serious complications from influenza infection is elevated in persons at both age extremes as well as in those with certain underlying conditions. The most common serious complications of influenza include exacerbation of underlying chronic pulmonary and cardiopulmonary diseases, such as chronic obstructive pulmonary disease, asthma, and congestive heart failure, as well as development of bacterial pneumonia, usually associated with *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Haemophilus influenzae*. Primary viral pneumonia occurs infrequently but is often fatal. New risk factors during the 2009 pandemic included those with morbid obesity and of aboriginal origin.

Influenza vaccines form the mainstay of public health and personal protection against circulating seasonal influenza viruses. Influenza virus antigenic drift required a robust global surveillance system which monitors emergence of new strains. The World Health Organization (WHO) biannually updates the latest recommended vaccine compositions for both the Northern and Southern hemispheres. Quadrivalent influenza vaccines incorporate influenza A/H1N1, A/H3N2 strains and 2 influenza B strains representing Victoria and Yagamata lineages.

Influenza

Vaccines

Most influenza vaccines are prepared in embryonated eggs. Cell culture influenza vaccine is produced in sterile incubators without use of eggs, antibiotics or preservatives.

Interest in the development of 'Universal' influenza vaccine focuses on identifying conserved proteins that are accessible to immune recognition.

Vaccines Available in Malaysia

Egg – Based Influenza Vaccine

1. Fluarix Tetra® (Inactivated influenza vaccine)
GlaxoSmithKline Pharmaceuticals (M) Sdn Bhd/GlaxoSmithKline Biologicals, Germany
2. Influvac® (Inactivated influenza vaccine)
Abbott Laboratories (M) Sdn Bhd/Abbott Biologicals B.V., Netherlands
3. FluQuadri Quadrivalent™
Sanofi Aventis (M) Sdn Bhd/Sanofi Pasteur Inc., USA
4. Vaxigrip Tetra®
Sanofi Aventis (M) Sdn Bhd/ Sanofi Pasteur inc., France

Cell-Based Influenza Vaccine

1. SKYCellflu Quadrivalent®
AJ Biologics (M) Sdn Bhd/SK Bioscience Co., South Korea

Mode of Administration

- Inactivated influenza virus vaccines have been given by intramuscular, subcutaneous, or intradermal routes. The routes associated with the most reproducible immunogenicity and lowest reactogenicity have been the intramuscular and subcutaneous routes.

- The intradermal route requires less antigen than intramuscular injection to produce a similar immunologic response, but it results in more local erythema at the injection site than other routes. An influenza vaccine using a micro-injection device and 9µg of each hemagglutinin (HA) per dose is now approved for use on those aged 18-59 years and 15µg per HA formulation is recommended for those ≥60 years old.

Co-administration with Other Vaccines

- Inactivated Influenza vaccine can be administered concurrently with other vaccines, including pneumococcal polysaccharide vaccine.

Contraindications and Adverse Effects

- Persons known to have an anaphylactic hypersensitivity to eggs or egg antigens or to influenza vaccine should not be vaccinated with an egg-replicated influenza vaccine until they are evaluated by a physician. Recombinant influenza vaccine may be given to persons with known egg allergies.

- The most common adverse effects are soreness at injection site, fever, myalgia and headache. Adjuvanted vaccine may be associated with more severe local reaction.

- Persons with history of Guillaine-Barre syndrome (GBS) occurring six weeks post vaccination is more likely to have subsequent GBS. It is not recommended for those with history of GBS to be vaccinated with influenza vaccine.

- To date, the most frequently reported adverse events for influenza vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) are local site reactions such as injection site pain and swelling, fever, flu-like syndrome, headache, fatigue and rash.

Target Groups in Malaysia

- Annual administration of influenza vaccine is indicated for anyone who wants to decrease the risk of influenza as well as the following target groups:

  » All healthcare workers

  » Persons at high risk of developing serious complications from influenza, including:

    ♦ All persons 50 years or older

    ♦ All persons aged 18-49 years with 1 or more medical conditions

    ♦ Pregnant women

    ♦ Persons living in certain institutional settings

    ♦ Obese persons

- Persons aged 50-59 years have been identified as a target group since approximately one third of them have a high-risk medical condition and age-based recommendations have been more successful than medical-condition-based recommendations in raising vaccination rates.

- Household members in close contact with persons with high-risk conditions, including out-of-home caregivers of children <6 months of age.

- Those performing religious pilgrimages, including the Hajj and Umrah.

Implications for Healthcare Workers (HCWs)

- All healthcare workers should receive annual influenza vaccination to reduce the risk of infection for themselves and their patients. This is regarded as an issue of patient safety.

- Influenza occurs all year round in Malaysia with peaks in May-July and November –January. Thus, both Southern and Northern formulations are used. The rule of thumb is to use the latest formulation available.

Evidence for Effectiveness

- A systematic review and meta-analyses of 31 influenza vaccine studies, against circulating influenza viruses confirmed by RT-PCR or virus culture, found a trivalent inactivated vaccine (TIV) pooled efficacy of 59%. Evidence for protection in adults aged 65 years or older is lacking.

- A study among Malaysian pilgrims attending the Hajj in Saudi Arabia found that adjusted vaccine effectiveness against clinic visits for influenza-like illness was 77% while that of recipients of antibiotics was 66%. Pilgrims traveling for the Hajj in Saudi Arabia should consider influenza vaccination.

- Elderly subjects generally respond less effectively to standard dose influenza vaccines than young healthy adults. Those with chronic debilitating medical conditions generally do not respond as effectively as healthy subjects of similar age. Up to 50% of elderly vaccinees may fail to respond to standard doses of inactivated influenza vaccine, with a 4-fold increase in hemagglutinin inhibition (HI) antibodies.

- A study on the effectiveness of influenza vaccination among inhabitants of homes for the elderly was conducted in Malaysia. The vaccine effectiveness in reducing the occurrence of influenza-like illness ranged from 55-76% during the 6-month study follow-up. Vaccine recipients had fewer episodes of fever, cough, muscle ache, runny nose ($p<0.001$) and experienced fewer sick days due to respiratory illness.

References

1. Bresee, J.S., Fry, A.M., Sambhara, S., Cox, N.J. (2018) Inactivated Influenza vaccine. In Plotkin S.A., Orenstein W.A., Paul A Offit, P.A. and Edwards K.M.(Eds). Vaccines. (7th Edition.) Saunders Elsevier.
2. Centers for Disease Control and Prevention. (2015) The Pink Book: Epidemiology and Prevention of Vaccine Preventable Diseases. 13 th Edition
3. Cox, M.M.J, Hashimoto, Y.(2011) A fast tract influenza vaccine virus produced in insect cells. J Inverteb Pathol, 107, Suppl, S31-41
4. Hui, L.S., Rashwan, H., Jaafar, M.H., Hussaini, M.H., Isahak, I.(2008) Effectiveness of influenza vaccine in preventing influenza-like illness among Faculty of Dentistry staff and students in Universiti Kebangsaan Malaysia. Health Care Infect,13(1) 4–9
5. I-Ching, S., Abdul-Murad, A., Karunakaran, R., Rampal, S., Chan, Y.F., Nathan, A.M., Ariffin, H. (2010) Clinical features of Malaysian children hospitalized with community-acquired seasonal influenza. Int J Infect Dis, 14S, 3,e36-e40
6. Isahak, I., Mahayiddin, A.A., Ismail, R. (2007) Effectiveness of influenza vaccination in prevention of influenza-like illness among inhabitants of old folk homes. Southeast Asian J Trop Med Public Health. ,38(5),841-8
7. Mustafa, A.N., Gessner, B.D., Ismail, R., Yusoff, A.F., Abdullah, N., Isahak, I., Abdullah, N., Merican, M.I.(2003) A case-control study of influenza vaccine effectiveness among Malaysian pilgrims attending the Haj in Saudi Arabia. Int J Infect Dis.,7(3),210-4
8. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia
9. Osterholm. M,T., Kelly, N.S., Sommer, A., Belongia, E.A.(2012) Efficacy and effectiveness of influenza vaccines: a systemic review and meta-analysis. Lancet Infect,12(1),36-44
10. Schultz-Cherry, S. Is it Possible? A Different Approach to Creating a Universal influenza vaccine. http://mbio.asm.org/content/6/5/e01580-15
11. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Received on 5 September 2019
12. The Malaysian National Centre of Adverse Drug Reactions Database. Accessed: 10 October 2019

Japanese Encephalitis

Introduction

Japanese encephalitis (JE), is a mosquito-borne viral infection of the central nervous system. Numerically it is the most important cause of viral encephalitis across Asia with an estimated 70,000 cases and 10,000 to 15,000 deaths annually. The causative agent, JE virus (genus *Flavivirus*, family *Flaviviridae*) is transmitted primarily among birds, pigs, and other vertebrate hosts by *Culex* species mosquitoes that breed in flooded rice fields and stagnant water and bites largely at dusk and night. While pigs and water birds serve as the main amplifying hosts, humans are merely incidental dead-end hosts that become infected when they encroach on the enzoonotic cycle. The viraemia that occurs during the prodromal period of JE virus infection in humans is too low to permit further transmission.

The virus is found in South East Asia, India, Nepal, China, Korea peninsula, Japan, Pacific islands Rim and northern Australia. There are two transmission patterns of JEV in three climatic zones: in temperate climate zones such as Japan, Korea and mainland China and Taiwan, and sub-tropical climate zones such as Nepal, and northerly areas of India, Thailand and Vietnam, JEV exhibits an epidemic or outbreak transmission pattern, characterised by a well-defined seasonal peak during the summer months. In tropical climate zones such as Malaysia, Indonesia, southerly areas of Vietnam and Thailand, JEV exhibits an endemic transmission characterised by sporadic human cases throughout the year with seasonal peaks that coincides with high rainfall during the monsoon season.

In parts of Asia where JE is endemic, it is primarily a disease of children living in rural areas. Whilst most people living in endemic areas are infected by the age of 15 years, JE virus can infect all age groups, particularly when it is newly introduced into geographical areas where the general population has no pre-existing immunity. Only 1 in 300 infections result in symptomatic illness. These may range from a non-specific flu-like illness, febrile seizures, aseptic meningitis, encephalitis and poliomyelitis-like acute flaccid paralysis.

Japanese Encephalitis

In endemic areas most cases of encephalitis occur in children, but travelers from non-JE endemic region are also at risk. There is no specific antiviral treatment for severe JE apart from supportive care. The acute case fatality rate of encephalitis is approximately 30%, and up to 50% of the survivors develop severe neurological sequelae. Although the clinical condition of many JE survivors improves during the first 3–6 months after hospital discharge, less than 50% make a full recovery, and about 20% experienced subsequent deterioration on long term follow-up.

In Malaysia, the great majority of laboratory-confirmed JE cases are found in Sarawak. There is a paucity of data on JE in other parts of Malaysia although 2 outbreaks have been recorded in peninsular Malaysia - Pulau Langkawi in 1974 (Fang et al. 1980) and Penang in 1988 (Cardosa et al. 1995).

Vaccines Available in Malaysia

1. IMOJEV® (Live attenuated recombinant chimeric JE vaccine, prM and E protein are derived from SA-14-14-2 vaccine strain)
Sanofi-Aventis (M) Sdn Bhd/Government Pharmaceutical Organisation-Merieux Biological Product Company Limited, Thailand
2. Japanese Encephalitis Vaccine® (Inactivated mouse brain derived JE vaccine, Nakayama strain)
Propharm (M) Sdn Bhd/Green Cross Corporation, South Korea
3. CD.JEVAX® (Live attenuated JE vaccine, SA-14-14-2 vaccine strain)
Farmaco Healthcare Sdn Bhd/Chengdu Institute of Biological Products, China

Mode of Administration

1. Live-attenuated recombinant chimeric JE vaccine (IMOJEV®)

   - Administration route: subcutaneous injection

     a. Children aged 9 months and above: a single injection. A booster dose should be given preferably 1-2 year after the first vaccination for those aged <18 years. No booster is recommended for adults.

2. Inactivated mouse brain-derived vaccine (Japanese Encephalitis Vaccine®)

   - Administration route: subcutaneous injection

     a. Individuals living in endemic areas: 2 primary doses (1.0 ml for those aged >3 years to adults, 0.5ml for those 1-3 years) at 4 weeks apart, followed by a booster 1 year after the primary series. Subsequent boosters are recommended at 3-year intervals up to the age of 15 years.

     b. For travelers aged >1 year visiting rural areas of endemic countries for >2 weeks: 3 primary doses at days 0, 7 and 28. When continual protection is required, boosters should be given after 1 year, subsequently every 3 years.

3. Live attenuated JE vaccine (CD.JEVAX®)

   - Administration route: subcutaneous injection

     a. Children aged 8 months and above: a single injection. No booster is required.

Co-administration with Other Vaccines

- JE vaccine is frequently co-administered with other vaccines on the immunisation schedule. Simultaneous administration of inactivated JE vaccine with measles, mumps, rubella vaccine did not result in reduced immunogenicity or increased side effects. JE vaccine can be given concurrently with the 4th dose of diphtheria, tetanus toxoids and pertussis (DTP) and, oral poliovirus vaccine at 18 months.

Contraindications and Adverse Effects

- **IMOJEV®** should not be administered to anyone with a history of severe allergic reaction to any component of the vaccines, after previous administration of the vaccine or any vaccine containing the same components or constituents. In adults, adverse effects following **IMOJEV®** were similar to those in placebo recipients, but occurred less often than in recipients of the mouse brain-derived JE vaccine. The most common adverse effects in two key studies were injection site pain, headache, fatigue and malaise. Most symptoms resolved within 3 days.

- Mouse brain-derived **Japanese Encephalitis Vaccine®** is contraindicated in people who have had an allergic reaction to the vaccine, gelatin or other rodent-derived products, including previous doses of JE vaccine. The most common adverse effects include local redness, pain, or swelling at the injection site.

- **CD.JEVAX®** should not be administered to persons with/on:

  - » a proven or suspected history of hypersensitivity/ anaphylactic reaction to any component of the vaccine, including gelatin.
  - » fever, acute infectious disease, tympanitis or active untreated tuberculosis.
  - » malnutrition, general allergy and convulsion.
  - » cardiac, liver or renal impairment.
  - » any type of immunosuppressive therapy.
  - » immune systems that are weak or not functioning properly.

As is the case with all medications, the administration of **CD.JEVAX®** can cause adverse reactions. Adverse reactions are observed in a small percentage of the vaccinees after administration of **CD.JEVAX®**. Some minor adverse effects, such as fever, rash, and nausea have been reported after injection but normally do not last longer than 2 days. Most are relieved spontaneously without requiring any particular treatment.

Target Groups in Malaysia

1. Workers, travelers and other individuals on an extended stay in Sarawak.

2. Research laboratory personnel who may potentially be exposed to field or virulent strains of the virus, as well as those who have contact with live swine (pig farmers and abattoir workers).

Note:

- Children in Sarawak receive live-attenuated recombinant chimeric JE vaccine (IMOJEV®) at 9 and 21 months under the Expanded Programme of Immunisation (EPI).

Evidence for Effectiveness

Human vaccination is the most effective measure in reducing the disease burden of JE in endemic areas. When a high rate of immunisation coverage is sustained in populations at risk, the incidence of JE could be reduced significantly despite the fact that the virus remains in circulation.

Studies have shown the use of inactivated mouse brain derived and live attenuated vaccines have reduced considerably the incidence of JE in Japan, Thailand, Nepal and Sarawak. The average annual incidence of JE in Sarawak prior to introduction of inactivated mouse brain derived vaccine into the EPI in 2001 was 9.8 cases per 100 000 population aged 12 years and below. By the end of 2006, the average annual incidence had dropped to 4.3 cases per

100 000 population aged 12 years and below. There is still no data on the population impact for live-attenuated recombinant chimeric JE vaccine yet.

It is pertinent to note that JEV is a zoonotic virus and humans are incidental dead-end hosts. Vaccination has no impact on the zoonotic transmission of the virus, hence susceptible individuals will continue to be at risk of disease even when few cases are observed. Thus any vaccination programme would have to target all susceptible individuals without expecting herd immunity to contribute to a reduction in incidence.

References

1. Bista, M. B., Banerjee, M., Shin, S. H., Tandan, J., Kim, M. H., Sohn, Y. M., . . . Halstead, S. B. (2001). Efficacy of single-dose SA 14–14–2 vaccine against Japanese encephalitis: A case control study. The Lancet, 358(9284), 791-795. doi:10.1016/s0140-6736(01)05967-0
2. Campbell, G., Hills, S., Fischer, M., Jacobson, J., Hoke, C., Hombach, J., Ginsburg, A. (2011). Estimated global incidence of Japanese encephalitis:. Bulletin of the World Health Organization, 89(10), 766-774. doi:10.2471/blt.10.085233
3. Gatchalian S, Yao Y, Zhou B, et al. (2006). Measles vaccine immunogenicity after coadministration with live attenuated
4. Halstead, S. B., Hills, S. L., & Dubischar, K. (2018). Japanese encephalitis vaccine. In 979245011 758798570 P. A. Offit, 979245012 758798570 W. A. Orenstein, & 979245013 758798570 S. A. Plotkin (Authors), Plotkin's vaccines (7th ed.). Philadelphia, PA: Elsevier.
5. Hennessy, S., Strom, B., Bilker, W., Zhengle, L., Chao-Min, W., Hui-Lian, L., . . . Halstead, S. (1996). Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): A case-control study. The Lancet, 347(9015), 1583-1586. doi:10.1016/s0140-6736(96)91075-2
6. Impoinvil, D. E., Ooi, M. H., Diggle, P. J., Caminade, C., Cardosa, M. J., Morse, A. P., Solomon, T. (2013). The Effect of Vaccination Coverage and Climate on Japanese Encephalitis in Sarawak, Malaysia. PLoS Neglected Tropical Diseases, 7(8). doi:10.1371/journal.pntd.0002334 Japanese encephalitis vaccine shows equivalence to that of measles vaccine given alone [abstract]. In: American Society of Tropical and Medicine and Hygiene 54th Annual Meeting. Atlanta (GA). 2605
7. Japanese Encephalitis Vaccines: WHO position paper (2006). (34/35), 81, 331-340.
8. Japanese Encephalitis Vaccines: WHO position paper. (2015). (9), 69-88, 90.
9. Monath, T., Guirakhoo, F., Nichols, R., Yoksan, S., Schrader, R., Murphy, C., . . . Bedford, P. (2003). Chimeric Live, Attenuated Vaccine against Japanese Encephalitis (ChimeriVax- JE): Phase 2 Clinical Trials for Safety and Immunogenicity, Effect of Vaccine Dose and Schedule, and Memory Response to Challenge with Inactivated Japanese Encephalitis Antigen. The Journal of Infectious Diseases, 188(8), 1213-1230. doi:10.1086/378356
10. Nasveld, P. E., Ebringer, A., Elmes, N., Bennett, S., Yoksan, S., Aaskov, J., . . . Reid, M. (2010). Long term immunity to live attenuated Japanese encephalitis chimeric virus vaccine. Human Vaccines, 6(12), 1038-1046. doi:10.4161/hv.6.12.13057The Malaysian National Centre of Adverse Drug Reactions Database. Accessed: October 10, 2019
11. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Received September 5, 2019.
12. Ohrr, H., Tandan, J., Sohn, Y. M., Shin, S. H., Pradhan, D. P., & Halstead, S. B. (2005). Effect of single dose of SA 14-14-2 vaccine 1 year after immunisation in Nepalese children with Japanese encephalitis: A case-control study. The Lancet, 366(9494), 1375-1378. doi:10.1016/s0140-6736(05)67567-8
13. Ooi, M., Lewthwaite, P., Lai, B., Mohan, A., Clear, D., Lim, L., . . . Solomon, T. (2008). The Epidemiology, Clinical Features, and Long- Term Prognosis of Japanese Encephalitis in Central Sarawak, Malaysia, 1997–2005. Clinical Infectious Diseases, 47(4), 458-468. doi:10.1086/590008
14. Sohn, Y. M., Park, M. S., Rho, H. O., Chandler, L. J., Shope, R. E., & Tsai, T. F. (1999). Primary and booster immune responses to SA14-14-2 Japanese encephalitis vaccine in Korean infants. Vaccine, 17(18), 2259-2264. doi:10.1016/s0264-410x(99)00006-7
15. The Malaysian National Centre of Adverse Drug Reactions Database. Accessed: October 10, 2019.
16. Torresi, J., Mccarthy, K., Feroldi, E., & Méric, C. (2010). Immunogenicity, safety and tolerability in adults of a new single-dose, live-attenuated vaccine against Japanese encephalitis: Randomised controlled phase 3 trials. Vaccine, 28(50), 7993-8000. doi:10.1016/j.vaccine.2010.09.035
17. Wong, S. C., Ooi, M. H., Abdullah, A. R., Wong, S. Y., Krishnan, S., Tio, P. H., Cardosa, M. J. (2008). A decade of Japanese encephalitis surveillance in Sarawak, Malaysia: 1997-2006. Tropical Medicine & International Health, 13(1), 52-55. doi:10.1111/j.1365-3156.2007.01967.x
18. Xin, Y. Y., Jian, A., Peng, G. Y., Min, L. H., & Ming, Z. G. (1988). Safety of a Live-Attenuated Japanese Encephalitis Virus Vaccine (SA14-14-2) for Children. The American Journal of Tropical Medicine and Hygiene, 39(2), 214-217. doi:10.4269/ajtmh.1988.39.214

Introduction

Measles is one of the most contagious viral infections affecting humans. The causative agent, measles virus (genus *Morbillivirus*, family *Paramyxoviridae*), is spread from human-to-human through air-borne respiratory droplets and direct contact with infected secretions. The disease is characterised by a prodromal stage of high grade fever, malaise, conjunctivitis, coryza and cough. One to two days before the onset of the characteristic morbilliform rash, multiple small whitish Koplik's spots resembling grains of salt, a pathognomonic sign for measles, may be found on the buccal mucosa, just opposite to the first or second molar, and remain visible for 1-2 days after the appearance of skin rash. The incubation period for the measles is about 10-14 days. The infectious period of symptomatic cases starts from 4 days before through 4 days after the onset of the rash. Disease transmission from an asymptomatic exposed immune person has not been documented. As humans are the only natural hosts for the virus, measles is preventable and can be eliminated by vaccination. Without vaccination, approximately 95% of the population would have acquired measles infection by 15 years of age. In settings where there is reduced virus transmission among the younger population following rising vaccination coverage in the population, adolescents and young adults may become the most susceptible population group if they have not been exposed to wild-type measles virus or had no prior measles vaccination.

The severity, complication risk and clinical outcomes of measles virus infection varies greatly, depending on the person's age, nutritional status and co-morbidities. The most common complications of measles are otitis media, pneumonia, croup, diarrhoea, post-infectious encephalitis and subacute sclerosing panencephalitis (SSPE). While young children are prone to develop severe life-threating pneumonia, either in the form of primary viral pneumonia or secondary bacterial pneumonia, adults aged >20 years are at risk of acute encephalitis. Measles infection in immunocompromised individuals, including the HIV infected, may have atypical presentation with no skin rash, and can be severe, prolonged and potentially fatal. Measles infection poses a special risk to susceptible females of reproductive age; it is associated with an increased risk of maternal, foetal, and neonatal

complications. Infected pregnant women are at a higher risk of hospitalisation, foetal loss, premature labour, pneumonia and maternal death compared to infected non-pregnant women. Intrauterine measles virus infection may range from a mild illness including low birth weight to a severe, fatal outcome. Measles virus infection is not associated with teratogenicity.

Vaccines

- A number of live-attenuated measles vaccines are available, either as monovalent vaccine or measles-containing vaccine (MCV) in combination with rubella, mumps or varicella vaccines or some combinations of these. When using the combined measles-rubella (MR) vaccine, measles-mumps-rubella (MMR) vaccine, or measles-mumps-rubella-varicella (MMRV) vaccine, the protective immune responses to each individual vaccine antigen as well as vaccine associated adverse events, remain largely unchanged. They are safe, effective and provide long-lasting immunity, and may be used interchangeably in immunisation programmes.

Vaccines Available in Malaysia

1. MMR II® (Live attenuated measles, mumps and rubella vaccine)
Merck Sharp & Dohme (Malaysia) Sdn Bhd/Merck Sharp & Dohme Corp. USA
2. Proquad® (Live attenuated measles, mumps and rubella plus varicella vaccine)
Merck Sharp & Dohme (Malaysia) Sdn Bhd/Merck Sharp & Dohme Corp. USA
3. Priorix® (Live attenuated measles, mumps and rubella vaccine)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

4. Priorix Tetra® (Live attenuated measles, mumps and rubella plus varicella vaccine)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
5. Measles vaccine® (Live attenuated measles vaccine)
Propharm (M) Sdn Bhd/PT Bio Farma
6. SII Measles Vaccine® (Live attenuated measles vaccine, single or 10 doses)
SM Pharmaceuticals Sdn Bhd/Serum Institute of India
7. Measles and Rubella® (Live attenuated measles and rubella vaccine)
Serum Institute of India/SM Biomed
8. SII Measles and Rubella Virus Vaccine® (Live attenuated measles and rubella vaccine, single or 10 doses)
SM Pharmaceuticals Sdn Bhd/Serum Institute of India

Mode of Administration

- Measles vaccine is generally injected subcutaneously, but it is also effective when administered intramuscularly.

Post-exposure Prophylaxis

- Measles vaccine may be used to protect susceptible individuals against measles if the vaccine is administered within 72 hours of the virus exposure. Timely administration of the vaccine is effective in preventing, shortening the duration or reducing the severity of the disease.

- In the event that measles vaccination is contraindicated (e.g. pregnant women, infants aged <6 months and immunocompromised individuals) or was not given within 72 hours of initial exposure, human immunoglobulin may be given within 6 days of the exposure to prevent measles or reduce the severity or duration of illness.

Co-administration with Other Vaccines

- Equal protection against measles is achieved when measles vaccine is used alone or in combined products such as measles-rubella (MR) vaccine or MMR. Immunogenicity and reactogenicity of the individual components are similar when MCVs are administered as combined products or simultaneously at different anatomical sites with other vaccines. These vaccines include diphtheria toxoid, tetanus toxoid, pertussis vaccine, Hib vaccine, oral polio vaccine or inactivated polio vaccine, varicella vaccine, hepatitis B vaccine, or pneumococcal vaccine. Vaccines against measles and yellow fever or Japanese encephalitis may be administered at the same time at different sites.

Contraindications and Adverse Effects

- Measles-containing vaccine should be given at least 2 weeks before the administration of blood products or deferred until 3 -11 months after such administration depending on the nature of the blood product as passively acquired antibodies can interfere with response to the vaccine. (Refer to Table 10.1 on page 113)

- Mild, concurrent infections are not considered a contraindication to vaccination, but it should be avoided if the patient has a high fever or other signs of serious disease.

- As a precautionary measure, measles vaccine, either alone or in combination, should be avoided during pregnancy. However, inadvertent administration of the vaccine during pregnancy should not be a reason for terminating the pregnancy.

- People with a history of an anaphylactic reaction to neomycin, gelatin or other components of the vaccine should not be vaccinated. Furthermore, measles vaccine is contraindicated in people who are severely immunocompromised due to congenital disease, severe HIV infection, advanced leukaemia or lymphoma, serious malignant disease, treatment with high-dose steroids, alkylating agents or antimetabolites, or those who receive immunosuppressive therapeutic radiation.

- Adverse reactions following measles vaccination are generally mild and transient. Slight pain and tenderness at the site of injection may occur within 24 hours; this is sometimes followed by a mild fever and local lymphadenopathy. There is an increased, albeit small, risk of febrile seizures following tetravalent measles-mumps-rubella-varicella vaccine when compared to concomitant administration of MMR and varicella vaccine in children aged 12-23 months when the vaccines are given for the first time. There was no increased risk of febrile seizures after the second dose of MMRV.

- Allergic reactions to vaccine components, including neomycin and the stabilisers gelatin or sorbitol, may occur post vaccination. Anaphylactic reactions are rare, occurring in 1/100,000 doses of vaccine administered.

- To date, the most frequently reported adverse events for the measles vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) are local site reactions such as injection site pain and swelling, fever, nausea and vomiting.

- Several well-conducted epidemiological studies have shown no link between the administration of measles vaccination and the development of inflammatory bowel disease or autism.

Measles

Target Groups in Malaysia

- Measles vaccine may be offered to teenagers and adults likely to be susceptible and at risk of being exposed to measles virus e.g. those who are travelling to measles endemic areas.

- College and university students: The risk for transmission of measles at these institutions is high due to large concentrations of persons who may be susceptible to measles. College entry requirements for measles immunity can substantially reduce the risk of measles outbreaks on college campuses where they are implemented and enforced. Therefore, colleges and universities should recommend that all undergraduate and graduate students have measles vaccination.

- All healthcare workers (HCWs) and any staff who are in regular contact with patients should be immune to measles. Transmission of measles virus in health-care settings affects both HCWs and patients. It poses a considerable risk to infants and immunocompromised individuals. It is recommended that all HCWs without history of measles or measles vaccination should be vaccinated.

- Measles vaccination should be routinely given to potentially susceptible, asymptomatic HIV-infected children and adults.

Evidence for Effectiveness

- A single dose of correctly administered measles vaccine will confer lifelong protection for most healthy individuals. The median vaccine effectiveness of a single dose of MCV administered at 9–11 months and >12 months old is 84% and 93%, respectively. Among children who do not respond to their first MCV dose, approximately 95% develop protective immunity after the second MCV dose.

Table 10.1
Recommended Intervals Between Immunoglobulins or Blood Products and MMR, MMRV or Varicella Vaccination

Immunoglobulin / blood product	Route	Dose (IU or ml)	Dose (estimated mg IgG/kg)	Interval (months)
Blood transfusion: Washed red cells	IV	10 ml/kg	Negligible	0
Blood transfusion: red cells, adenine-saline added	IV	10 ml/kg	10	3
Blood transfusion: packed red cells	IV	10 ml/kg	20-60	5
Blood transfusion: whole blood	IV	10 ml/kg	80-100	6
Plasma or platelet products	IV	10 ml/kg	160	7
Human immunoglobulin: immune thrombocytopenia purpura	IV	na	400	8
Human immunoglobulin: immune thrombocytopenia purpura	IV	na	1000	10
Human immunoglobulin: immune thrombocytopenia purpura or Kawasaki disease	IV	na	1600-2000	11

Measles

Immunoglobulin / blood product	Route	Dose (IU or ml)	Dose (estimated mg IgG/kg)	Interval (months)
Human immunoglobulin: measles prophylaxis (standard contact)	IM	0.2 ml/kg (maximal dose 15ml)	na	5
Human immunoglobulin: measles prophylaxis (immunocompromised contact)	IM	0.5 ml/kg (maximal dose 15ml)	na	6
Human immunoglobulin: replacement therapy for immunodeficiency	IV	na	300-400	9
Human immunoglobulin: Hepatitis A prophylaxis	IM	0.5 ml (<25kg) 1.0 ml (25-50kg) 2.0 ml (>50kg)	na	3
Hepatitis B immunoglobulin as hepatitis B prophylaxis	IM	100 or 400 IU	10	3
Cytomegalovirus immunoglobulin	IV	3 ml/kg	150	6
Human rabies immunoglobulin as rabies prophylaxis	IM	20 IU/kg	22	4

Immunoglobulin / blood product	Route	Dose (IU or ml)	Dose (estimated mg IgG/ kg)	Interval (months)
Zoster immunoglobulin as varicella prophylaxis	IM	200 IU (0–10kg) 400 IU (11–30kg) 600 IU (>30kg)	na	5
Tetanus immunoglobulin as tetanus prophylaxis	IM	250 IU (given within 24 hours of injury)	10	3
Tetanus immunoglobulin as tetanus prophylaxis	IM	500 IU (> 24 hours after injury)	20	3
Rh (D) immunoglobulin (anti-D)	IM	na	na	0

Adapted from: https://immunisationhandbook.health.gov.au/resources/handbook-tables/table-recommended-intervals-between-immunoglobulins-or-blood-products-and (last accessed on 22 May 2019)

References

1. The Malaysian National Centre of Adverse Drug Reactions Database. Accessed August 6, 2014.
2. Measles vaccines: WHO position paper (2017). 17, 205-228.
3. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Received December 16, 2013.
4. Strebel, P.M., Papania, M.J., Fiebelkorn AP and Halsey, N.A. (2018). Measles vaccine in Stanley Plotkin, Walter Orenstein and Paul Offit (7th Ed). Vaccines. PA: Elsevier.

Mumps

Introduction

Mumps is a mild childhood infection most commonly affecting children aged between 5 and 9 years old. It is caused by a mumps virus (genus Rubulavirus, family *Paramyxoviridae*) and transmitted from human to human through direct contact or by airborne droplets. Individuals with mumps are contagious from 2 days before, through 9 days after the onset of parotid swelling. The initial clinical features include fever, malaise, headache, and the characteristic parotid swelling. Mumps may also affect adults who are at a higher risk of complications such as meningitis, orchitis and hearing loss. Very rarely, encephalitis with long term neurological sequalae (including paralysis, seizures and cranial nerve palsies) may occur. Orchitis occurs in a fifth of post-pubertal males who develop mumps. In 20% of orchitis cases, both testes are affected, but mumps orchitis is rarely associated with permanently impaired fertility. Symptomatic oophoritis and mastitis are relatively uncommon and apparently without long-lasting consequences. Acquisition of mumps during the first 12 weeks of pregnancy is associated with a 25% incidence of spontaneous abortions, but foetal malformations following mumps virus infection during pregnancy have not been reported. Pancreatitis is reported as a complication in approximately 4% of cases, but the relationship between mumps, pancreatitis and diabetes mellitus remains speculative.

Vaccines

- A number of live-attenuated mumps vaccines are available, in the form of combination vaccine with measles, rubella, or varicella vaccines or some combination of these. When using the combined measles-mumps-rubella (MMR) vaccine, or measles-mumps-rubella-varicella (MMRV) vaccine, the protective immune responses to each individual vaccine antigen as well as vaccine associated adverse events, remain largely unchanged. They are safe, effective and provide long-lasting immunity.

Vaccines Available in Malaysia

1. MMR II®
(Live attenuated measles, mumps and rubella vaccine)
Merck Sharp & Dohme (Malaysia) Sdn Bhd/Merck Sharp & Dohme Corp. USA

2. Proquad®
(Live attenuated measles, mumps and rubella plus varicella vaccine)
Merck Sharp & Dohme (Malaysia) Sdn Bhd/Merck Sharp & Dohme Corp. USA

3. Priorix®
(Live attenuated measles, mumps and rubella vaccine)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

4. Priorix Tetra®
(Live attenuated measles, mumps and rubella plus varicella vaccine)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium

5. SII Measles, Mumps and Rubella Virus Vaccine®
(Live attenuated measles, mumps and rubella vaccine, single or 10 doses)
SM Pharmaceuticals Sdn Bhd/Serum Institute of India

Mode of Administration

- Mumps vaccines are administered subcutaneously.

Co-administration with Other Vaccines

MMR can be administered simultaneously with diphtheria, tetanus toxoids and acellular or whole-cell pertussis vaccine (DTaP/DTP), oral or inactivated poliovirus vaccine, *H. influenzae* type b conjugate vaccine, hepatitis B vaccine, or live attenuated influenza vaccine without impairing antibody responses

or increasing rates of serious adverse events. There is an increased, albeit small, risk of febrile seizures following tetravalent measles-mumps-rubella-varicella vaccine when compared to concomitant administration of MMR and varicella vaccine in children aged 12-23 months when the vaccines are given for the first time. There was no increase in febrile seizures after the second dose of MMRV.

Contraindications and Adverse Effects

- Caution should be exercised when administering MMR to people who have a history of an anaphylactic reaction to gelatin or gelatin-containing products.
- Those who have a history of anaphylactic reactions to neomycin should not receive the vaccine; a history of contact dermatitis to neomycin is not a contraindication to vaccination.
- Mumps-containing vaccine should be given at least 2 weeks before the administration of blood products or deferred until 3 -11 months after such administration, depending on the nature of the blood product as passively acquired antibodies can interfere with response to the vaccine. (Refer to Table 10.1 on page 113)
- Mumps-containing vaccine should not be given to pregnant women because of the theoretical risk of foetal damage. Likewise, vaccinated women should avoid pregnancy for 1 month after vaccination.
- MMR or MMRV vaccine should not be given to people with acquired immunocompromised immunity (leukemia, lymphoma, generalised malignancy, or therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation).
- Aside from low-grade fever, the most common adverse reaction to mumps vaccination is parotitis, occurring in less than 1-3% of vaccines. Orchitis, pancreatitis and sensorineural deafness following mumps vaccination are rare and encephalitis following vaccination does not occur more frequently than the background rate in the normal population.

- To date, the most frequently reported adverse events for MMR vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) are pyrexia, maculo-papular rash and pruritus.

Target Groups in Malaysia

- MMR vaccine is recommended for all children and for certain high-risk groups of adolescents and adults including travelers, university and college students.

- All healthcare workers (HCWs) and any staff who are in regular contact with patients should be immune to mumps. Transmission of mumps in health-care settings affects both HCWs and patients. It is recommended that all HCWs without history of mumps or mumps vaccination should be vaccinated.

Evidence for Effectiveness

- In studies of trivalent formulations with measles and rubella vaccines, seroconversion following administration of MMR containing the Jeryl Lynn strain ranged between 90% and 98%.

- Serologic studies show that neutralising antibodies remain for at least 12 years after vaccination.

References

1. The Malaysian National Centre of Adverse Drug Reactions database. Accessed October 10, 2019.
2. Mumps Vaccines Mumps virus vaccines. WHO position paper (2007). WHO Weekly Epidemiol Record 82: 49-60
3. National Pharmaceutical Regulatory Agency (NPRA),, Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Updated September 5, 2019
4. Rubin, S.A. & Plotkin, S.A. (2018). Mumps vaccine in Stanley Plotkin, Walter Orenstein and Paul Offit.
5. Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP) for the Control and Elimination of Mumps. (2006). PsycEXTRA Dataset, 55(22), 629-630. doi:10.1037/e566472006-004 Vaccines. (7th Ed). PA: Elsevier.

Rubella

Introduction

Rubella, also known as German measles, is a common febrile exanthema of children and young adults. The causative agent, rubella virus (genus Rubivirus family *Togaviridae*) is transmitted from person-to-person through respiratory droplets. Humans are the only known natural hosts to the virus. The incubation period of the disease is 2-3 weeks. The infected individuals become infectious a week before, through 2 weeks after the onset of maculopapular rash. Apart from the fever and often pruritic skin rash, the disease is characterised by malaise, conjunctivitis and arthralgia or arthritis, which is most commonly observed in adult women. Lymph node enlargement involving post-auricular, occipital and posterior cervical groups is characteristic and precedes the rash onset by 5 to 10 days. Up to 50% of rubella infection may occur without skin rash. While rubella is a mild self-limiting illness during childhood, it poses a special risk to women of child-bearing age due primarily to the virus teratogenicity, which forms the primary basis for universal rubella vaccination. Infection that occurs just before conception and during the first trimester of the pregnancy may result in foetal loss or congenital rubella syndrome. Beyond this period, foetal malformation is rare although isolated sensorineural hearing loss may occur up to 20 weeks of gestation. Congenital rubella syndrome comprises a broad range of multi-systemic defects, including abnormalities affecting eyes (cataracts, chorioretinitis, microphthalmia, glaucoma), sensorineural deafness, heart (patent ductus arteriosus, peripheral pulmonic artery stenosis, ventricular septal defects), brain (encephalitis, microcephaly, cognitive impairment), intrauterine growth retardation, hepatitis, hepatosplenomegaly, thrombocytopenic purpura, pneumonitis, endocrine disorders (diabetes, hypothyroidism) and autism in later life. Infants with congenital rubella may have prolonged viral shedding for a year or longer in throat secretions and urine.

Vaccines

- A number of live-attenuated rubella vaccines are available, either as monovalent or rubella-containing vaccine, in combination with measles (MR), measles and mumps (MMR) or measles, mumps and varicella (MMRV). The protective immune responses to each individual vaccine antigen as well as vaccine associated adverse events, remain largely unchanged. They are safe, effective and provide long-lasting immunity.

Vaccines Available in Malaysia

1. Rubella® (Live attenuated rubella vaccine)
SM Pharmaceuticals Sdn Bhd/Serum Institute of India
2. Measles and Rubella® (Live attenuated measles and rubella vaccine)
SM Pharmaceuticals Sdn Bhd/Serum Institute of India
3. MMR II® (Live attenuated measles, mumps and rubella vaccine)
Merck Sharp & Dohme (Malaysia) Sdn Bhd/Merck Sharp & Dohme Corp. USA
4. Proquad® (Live attenuated measles, mumps and rubella plus varicella vaccine)
Merck Sharp & Dohme (Malaysia) Sdn Bhd/Merck Sharp & Dohme Corp. USA
5. Priorix® (Live attenuated measles, mumps and rubella vaccine)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
6. Priorix Tetra® (Live attenuated measles, mumps and rubella plus varicella vaccine)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals S.A., Belgium
7. SII Measles and Rubella Virus Vaccine® (Live attenuated measles and rubella vaccine, single or 10 doses)
SM Pharmaceuticals Sdn Bhd/Serum Institute of India

Rubella

Mode of Administration

- Rubella containing vaccine is normally administered subcutaneously, but it is also effective when administered intramuscularly.

- A single dose of rubella vaccine provides high response rate (≥95%) and long-term persistence of immunity. While in theory a second dose of rubella vaccine is not required, it is nonetheless routinely given based on the indications for a second dose of measles and mumps-containing vaccines in most settings.

Co-administration with Other Vaccines

- Rubella or rubella-containing vaccine can be given simultaneously, but at a separate site, with diphtheria and tetanus toxoids and pertussis vaccine, *H. influenzae* vaccine, IPV, hepatitis B vaccine, OPV and varicella vaccine.

Contraindications and Adverse Effects

- Blood Products: Rubella containing vaccines should be given at least 2 weeks before the administration of blood products or deferred until 3 -11 months after such administration, depending on the nature of the blood product as passively acquired antibodies can interfere with response to the vaccine (refer to Table 10.1 on page 113). However, anti-Rho(D) globulin does not interfere with vaccination of postpartum women. Women who are vaccinated after receiving anti-Rho (D) globulin should be tested 6 weeks later for rubella antibodies.

- Pregnancy: Based on a theoretical, yet never proven, risk of teratogenicity, pregnant women should not receive rubella vaccination. Women who plan to conceive should be advised to delay the pregnancy for 1 month following rubella vaccination. However, inadvertent rubella vaccination of unknowingly pregnant women is not an indication for termination of pregnancy.

- Common side effects: vaccinees sometimes develop mild rubella, including rash, lymphadenopathy, fever, sore throat and headache as well as mild local reactions (pain, redness and induration). The incidence varies directly with age, being almost absent in infants but present in up to 50% of women. While joint-related symptoms are rarely reported in children and in men, arthralgia and arthritis may occur 7–21 days post-vaccination and last up to 2 weeks in adult women. Epidemiological studies have not demonstrated an association between rubella vaccine and chronic joint disease. There is an increased, albeit small, risk of febrile seizures following tetravalent measles-mumps-rubella-varicella vaccine when compared to concomitant administration of MMR and varicella vaccine in children aged 12–23 months when the vaccines are given for the first time. There was no increase in febrile seizures after the second dose of MMRV.

- Individuals with a history of an anaphylactic reaction to neomycin, gelatin or other components of the vaccine should not be vaccinated. Rubella vaccines should not be given to immunocompromised or immunosuppressed individuals including advanced HIV infection and AIDS, primary immunodeficiency, malignancies and aggressive immunosuppressive therapy.

- To date, the most frequently reported adverse events for rubella vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) include malaise, vomiting and rash.

Target Groups in Malaysia

- All adult females especially of childbearing age

- College and university students

- Healthcare workers

Rubella

Evidence for Effectiveness

Internationally licensed rubella vaccines, either single or in combinations, have proven highly efficacious in the prevention of rubella and congenital rubella syndrome worldwide. In outbreak situations the effectiveness of different rubella vaccines has been found to be 90–100% effective. The vaccine provides life-long immunity against rubella virus.

References

1. The Malaysian National Centre of Adverse Drug Reactions Database. Accessed October 10, 2019
2. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Updated September 5, 2019.
3. Plotkin, S.A. & Reed, S.E. (2018). Rubella vaccine in Stanley Plotkin, Walter Orenstein and Paul Offit. (7th Ed) Vaccines. PA: Elsevier
4. Rubella vaccine: WHO position paper (2011). WHO Weekly Epidemiological Record No 29, 86:301-316

Introduction

Meningococcal disease is most commonly manifested as meningitis or sepsis but can also present as septic arthritis or pneumonia. The case fatality varies from 7% for meningitis to as high as 19% for meningococcaemia without meningeal involvement. On the other hand, meningococci colonise the nasopharynx of 5-11% of adults and up to 25% of adolescents. The carriage rate is low in infants and young children.

Based on surface polysaccharide, *Neisseria meningitidis*, the causative organism, is divided into 13 serogroups of which serogroups A, B, C, X, Y, Z, W135 and L, have been associated with invasive disease. Serogroup A and C are the main cause of epidemic meningococcal meningitis. Serogroup B is generally associated with sporadic disease but may cause some upsurges or outbreaks. Serogroup W135 has caused international outbreaks in 2000 and 2001 among Hajj pilgrims and household contacts of returning pilgrims. Studies in the UK and US have revealed that students, in their first year of college and who are living in dormitories are at a higher risk of meningococcal disease, compared to other college students and age matched general population.

Vaccines

- Currently, tetravalent vaccines protecting against A, C, Y and W135 are available. These vaccines are derived from the capsular polysaccharide and can be either conjugated to diphtheria/tetanus toxoid or CRM197 (a non-toxic protein of *Corynebacterium diphtheriae*). These vaccines offer no protection against serogroup B organisms.

- A vaccine against serogroup B meningococcal disease is used in some countries but it is not currently available in Malaysia. It is a multicomponent vaccine made from three *N. meningitidis* proteins and capsular group B outer membrane vesicles.

Meningococcal

Vaccines Available in Malaysia

- Quadrivalent (ACWY) conjugate vaccine

1. Menactra® (serogroups A, C, W135 and Y polysaccharides conjugated with diphtheria toxoid protein)
Sanofi Aventis (M) Sdn Bhd/Sanofi Pasteur, US
2. Menveo® (serogroups A, C, W135 and Y polysaccharides conjugated with non-toxic *C. diphtheriae* CRM197 protein)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Vaccines, Italy
3 Nimenrix® (serogroups A, C, W135 and Y polysaccharides conjugated tetanus toxoid carrier proteins)
Pfizer (M) Sdn Bhd/Pfizer, Belgium

Mode of Administration

1. Persons with high-risk medical conditions such as functional or anatomical asplenia or complement component disorders, need a 2-dose primary schedule, approximately 8 weeks apart. They should also receive a conjugate vaccine at 5-yearly intervals.
2. Persons at risk of meningococcal diseases such as laboratory personnel or those travelling to parts of the world where epidemics of group A, W135 or Y disease are frequent, should receive a single dose of quadrivalent conjugate vaccine every 5 years if still at risk of meningococcal exposure.
3. The different conjugate vaccine products can be used interchangeably for the booster doses.
4. If Menactra® is used, it should be administered at least four weeks after completion of all pneumococcal conjugate vaccine doses.

Target Groups in Malaysia

- Pilgrims attending the Hajj or Umrah in Saudi Arabia. Saudi Arabian authorities require a valid certificate of vaccination, within the past 2-3 years, as a condition to enter the country. Accompanying children aged ≤2 years should receive the full course of conjugated meningococcal vaccine (ie Menactra® or Nimenrix®).

- Laboratory staff who frequently handle *N. meningitidis* isolates.

- Travelers who intend to visit parts of the world where epidemics of group A, W135 or Y disease are frequent (a current list of those countries is available at either www.who.int/ith or www.who.int/disease-outbreak-news).

- Adults with high-risk medical conditions, such as functional or anatomical asplenia or complement component disorders (C5-C9, properdin, factor D or factor H), persons receiving treatment with eculizumab (a monoclonal antibody directed against complement component C5), or those post-haematopoietic stem cell transplantation.

- Vaccination can be used in conjunction with chemoprophylaxis during outbreaks for close (household or household-like) contacts, aged ≥9 months, if the outbreak is due to A, C, Y or W135 serogroups.

Note:

- Certain groups of adolescents (15-19 years old) e.g military and police recruits, schools/college/university students who live in hostels are at higher risk of contracting meningococcal disease. In many countries, routine meningococcal vaccination is recommended in these groups.

Contraindications and Adverse Effects

- Vaccination should be avoided during acute febrile illnesses. It is contraindicated in persons with previous serious reactions to the vaccine or its components. For the conjugate vaccines, adverse reaction is generally mild with pain and redness at the injection site, fever, headache, anorexia and nausea. While there were initial concerns regarding Guillain-Barré syndrome (GBS) with Menactra®, recent safety studies found no increased risk in general population of those with history of GBS. Meningococcal vaccines are not routinely recommended for pregnant or breastfeeding women but can be given if clinically indicated.

- To date, the most frequently reported adverse events for meningococcal vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) include local site reactions such as injection site rash and tenderness, fever, muscle pain and rash.

Evidence of Effectiveness

The meningococcal conjugate vaccines elicit a T cell-dependent memory response that results in an improved primary response to vaccination and a strong anamnestic response at re-exposure when compared with polysaccharide vaccines. The effectiveness of Menactra® has been estimated to be 80-85%. However, the effectiveness seems to wane with time. Five years post vaccination, the proportion with protective antibody levels drop to 56-72% among adolescents.

References

1. Andersen, B.M. (1978) Mortality in meningococcal infections. Scand J of Infect Dis.;10(4):277-8.
2. Bruce, M.G., Rosenstein, N.E., Capparella J.M., Shutt K.A., Perkins B.A., Collins M. (2001) Risk factors for meningococcal disease in college students. JAMA;286(6):688-93
3. Cohn, A.C., MacNeil, J.R., Clark, T.A., Ortega-Sanchez, I.R., Briere, E.Z., Meissner, H.C., et al. (2013) Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunisation Practices (ACIP). MMWR Recommendations and reports: MMWR. Recommendations and reports / Centers for Disease Control. 62(Rr-2):1-28
4. Keyserling, H., Papa, T., Koranyi, K., Ryall, R., Bassily, E., Bybel, M.J., et al (2005). Safety, immunogenicity, and immune memory of a novel meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV-4) in healthy adolescents. Arch Pediatr Adolesc Med. 159(10):907-13
5. Macneil, J.R., Cohn, A.C., Zell, E.R., Schmink, S., Miller, E., Clark, T., Messonnier, N.E. (2011). Active Bacterial Core surveillance (ABCs) Team and MeningNet Surveillance Partners. Early estimate of the effectiveness of quadrivalent meningococcal conjugate vaccine. Pediatr Infect Dis J. 30(6):451-5
6. The Malaysian National Centre of Adverse Drug Reactions Database [Accessed: 10 October 2019]
7. Meningococcal disease, serogroup W135. Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations. Wkly Epidemiol Rec/Health Section of the Secretariat of the League of Nations. 2001;76(19):141-2
8. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Received on September 5, 2019.
9. Nelson, S.J., Charlett, A., Orr, H.J., Barker, R.M., Neal, K.R., Taylor, C., et al (2001). Risk factors for meningococcal disease in university halls of residence. Epidemiol Infect.126(2):211-7
10. Warshawsky, T.S.W.P.B.D.B. (2013). UPDATE ON THE USE OF QUADRIVALENT CONJUGATE MENINGOCOCCAL VACCINES: An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI). Can Commun Dis Rep. 39 (ACS-1):1-40.
11. Wilder-Smith, A., Barkham, T.M., Ravindran, S., Earnest, A., Paton, N.I. (2003) Persistence of W135 Neisseria meningitidis carriage in returning Hajj pilgrims: risk for early and late transmission to household contacts. Emerg Infect Dis. 9(1):123-6

Pneumococcal

Introduction

Streptococcus pneumoniae (pneumococcus) is a leading cause of pneumonia, bacteraemia, meningitis, otitis media and sinusitis. It is an encapsulated organism and the capsular polysaccharide is its most important virulence factor. Ninety one serotypes have been identified based on antigenic differences in their capsular polysaccharides, 15 of which cause the majority of diseases. Type-specific antibody to this capsular polysaccharide is protective.

Vaccines

- There are 2 different types of pneumococcal vaccines – pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPV).

1. Pneumococcal conjugate vaccine (PCV)
a. While there are 2 conjugate vaccines available in Malaysia, PCV 10 and PCV 13, only the latter is approved for adult use.
b. PCV 13 contains polysaccharide capsular antigens for 13 serotypes. The antigens are individually conjugated to diphtheria CRM197 conjugate protein, with aluminium phosphate used as an adjuvant.
c. PCV 10 contains polysaccharide capsular antigens for 10 serotypes. The antigens are individually conjugated to tetanus and diphtheria toxoid protein, with aluminium phosphate used as an adjuvant

2. Pneumococcal polysaccharide vaccine (PPV)
a. PPV23 contains pneumococcal capsular polysaccharides of 23 serotypes.

Vaccine	Serotypes in Pneumococcal Vaccine																							
	4	9V	6B	14	18C	19F	23F	1	5	7F	3	6A	19A	2	8	9N	10A	11A	12F	15B	17F	20	22F	33F
PCV13	•	•	•	•	•	•	•	•	•	•	•	•	•											
PPV23	•	•	•	•	•	•	•	•	•	•	•		•	•	•	•	•	•	•	•	•	•	•	•

Serotype distribution and vaccine coverage

Based on a review of 7 studies, which included 484 isolates causing IPD in Malaysia among all age groups, vaccine coverage for PCV 13 is estimated to be 75%. The estimated coverage for PPV23 is also similar (73%)

PCV reduces nasopharyngeal colonisation, thereby decreasing the spread of infection. Hence serotype distribution in adults is likely to change when pneumococcal conjugate vaccine is introduced into our national immunisation program. In countries with childhood vaccination coverage of >50%, the rate of invasive pneumococcal disease (IPD) in adults has decreased by 28% and rates of IPD due to strains covered by PCV13 has decreased by 40%. However, this has been accompanied by a 20% increase in IPD due to non-PCV13 strains in the elderly.

Vaccines Available in Malaysia

- Polysaccharide vaccine (PPV)

1. Pneumovax 23®

Merck Sharp & Dohme (M) Sdn Bhd/Merck Sharp & Dohme, US

- Conjugate vaccine (PCV)

1. Prevenar 13® (PCV13)

Pfizer (M) Sdn Bhd/Pfizer, Ireland

2. Synflorix® (PCV10)

GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline, Belgium

Table 12.1
Target Groups in Malaysia and Dosing Recommendations

Clinical risk groups	Explanations	Dosing recommendations
1. Adults with immunocompromising conditions with high risk of IPD		PCV13-PPV23 sequence -preferred (Fig 1a)[2, 3] 1. 1 dose of PCV13 vaccine 2. 1 dose of PPV23 vaccine at least 8 weeks after PCV13 vaccine 3. Booster doses of PPV23 vaccine at least 5 years after the last PPV23 vaccine 4. A final dose of PPV23 is given at least 5 years later or at age 60 years, whichever is later PPV23-PCV13 sequence (fig 1b): 1. If the individual has received PPV23 vaccine before, PCV13 vaccine should be administered at least 1 year after the previous dose of PPV23
a. Asplenia or dysfunction of the spleen	Includes conditions such as homozygous sickle cell disease and coeliac syndrome	
b. Hematological and other malignancies	Includes generalised malignancy, leukemia or lymphoma, multiple myeloma	
c. Solid organ transplant		
d. Immunosuppressive therapy	On or likely to be on steroids at a dose equivalent to prednisolone 20mg or more per day for more than a month, chemotherapy, radiation therapy	
e. HIV infection		
f. Congenital or acquired immunodeficiency		
2. Individuals with cochlear implants		
3. Individuals with CSF leaks and CSF shunts	Includes leakage of CSF following trauma or major skull surgery	

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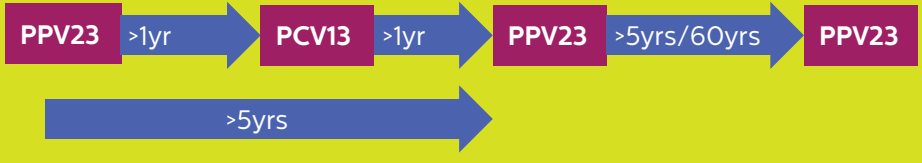
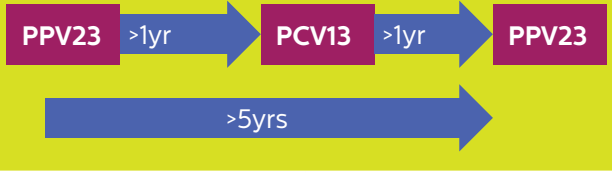
Clinical risk groups	Explanations	Dosing recommendations
4. Chronic kidney disease	Includes nephrotic syndrome, chronic kidney disease at stages 4&5 and those on dialysis.	2. 2nd dose of PPV23 vaccine at least 5 years after the last PPV23 vaccine 3. A final dose of PPV23 is given at least 5 years later or at age 60 years, whichever is later.
Fig 1a  Fig 1b  		
5. Hematopoietic stem cell transplant recipient (refer to page 255)		
6. Adults with pre-existing medical conditions (18–59 years)		
a. Chronic heart disease	Includes chronic heart failure, hypertension with cardiac complications, congenital heart disease and ischemic heart disease	1 dose of PPV23 vaccine

Clinical risk groups	Explanations	Dosing recommendations
b. Chronic liver disease	Includes cirrhosis, biliary atresia and chronic hepatitis	1 dose of PPV23 vaccine
c. Diabetes	Requiring oral hypoglycaemics agents or insulin	
d. Chronic respiratory disease	Includes chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung disease, pneumoconiosis, and bronchopulmonary dysplasia. Asthma is not an indication unless continuous steroids or frequently repeated systemic steroids are required (as defined in immunosuppressive therapy above)	
7. All adults at 60 years or above	Includes healthy adults and adults with pre-existing medical conditions as in group 6 above.	PCV13-PPV23 sequence-preferred (Fig 2)[2, 3] 1. 1 dose of PCV13 vaccine at least 1 year after any previous dose of PPV23

Clinical risk groups	Explanations	Dosing recommendations
		2. 1 dose of PPV23 vaccine at least 1 year after PCV13 vaccine and at least 5 years after any previous dose of PPV23 Alternative: 1 dose of PPV23 vaccine
Fig 2  		
8. Persons going for religious pilgrimage (e.g., Hajj)	For those with pre-existing medical conditions or age >60 years, follow recommendations as per their risk group	1 dose of PPV23 vaccine

Notes:
1. Intervals Between PCV13 and PPV23 Vaccines
   PCV 13 - PPV23 sequence – For Group 1- 4 above - > 8 weeks;
   for others if required - > 1 year
   PPV23 – PCV 13 sequence - > 1 year
2. The minimum interval between any 2 doses of PPV23 is 5 years.
3. It is recommended for adults to receive no more than 3 doses of PPV23.

Sequential dose of Pneumococcal vaccines

In PPV23-naive and PPV23-preimmunized adults, PCV13 should be given first if both vaccines are to be given. In PPV23-naive adults, PCV13 improves the antibody response to subsequent PPV23 vaccination. Interval between vaccine administrations also may be critical to obtaining an optimal immunological effect. Longer intervals (ie, ≥ 1 year) may lead to improved immune responses against serotypes in both vaccines.

Coadministration with Other Vaccines

Pneumococcal vaccines can be administered concomitantly with influenza vaccines but at separate sites.

Co-administration of Menactra® (Quadrivalent (ACWY) conjugate vaccine) with PCV13 should be avoided. This is because Menactra may interfere with the immune response against some pneumococcal serotypes. Menveo or Nimenrix can be co-administered with PCV13. If needed to be co-administered, administer Menactra 4 weeks after PCV13.

Contraindications and Adverse Events

- Contraindications to pneumococcal vaccines include anaphylaxis following a previous dose of any pneumococcal vaccine and persons with moderate or severe acute illness at the time of vaccination. However, minor illnesses such as upper respiratory infections are not a contraindication to vaccination.

- Data on the use of conjugate vaccine (PCV) during pregnancy and lactation is not available. For high-risk patients, it is recommended to administer PCV, either before a planned pregnancy or after delivery and cessation of breastfeeding.

- The safety of polysaccharide vaccine (PPV) for pregnant women has not been studied; however no adverse events have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. Similar to PCV, it is recommended to give PPV before a planned pregnancy or soon after delivery in high-risk individuals. PPV may be given to breastfeeding women.

- Local reactions include pain, redness and induration which usually last less than 48 hours. Systemic reactions such as fever, rash, myalgia and headache are uncommon. Severe reactions such as serum sickness and anaphylaxis are extremely rare.

- To date, the most frequently reported adverse events for pneumococcal vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) include local site reactions such as injection site pain and swelling, fever, muscle pain and skin rash.

Evidence of Effectiveness

A meta-analysis found strong evidence of PPV efficacy against invasive pneumococcal disease in adults. There was efficacy against all-cause pneumonia in low-income but not high-income countries. However, PPV was not associated with substantial reductions in all-cause mortality. Vaccine efficacy against primary outcomes, seemed poorer in adults with chronic illness.

Six randomised controlled studies evaluated immunogenicity and safety of PCV13 in adults and showed that the conjugated vaccine elicited a greater immune response to the majority of the 13 serotypes compared to the PPV23.

Results of the CAPiTA trial conducted in Netherlands among 85,000 adults aged ≥65 years demonstrated 45.6% (95% CI = 21.8%-62.5%) efficacy of PCV13 against vaccine-type pneumococcal pneumonia, 45.0% (CI = 14.2%–65.3%)

efficacy against vaccine-type nonbacteraemic pneumococcal pneumonia, and 75.0% (CI = 41.4%–90.8%) efficacy against vaccine-type IPD among adults aged ≥65 years.

References

1. Bonten, M.J.,et al (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med;372(12):1114-25.
2. Jauneikaite, E., Jefferies, J.M., Hibberd, M.L., Clarke, S.C. (2012). Prevalence of Streptococcus pneumoniae serotypes causing invasive and non-invasive disease in South East Asia: a review. Vaccine. 30(24):3503-14
3. The Malaysian National Centre of Adverse Drug Reactions Database [Accessed: October 10, 2019]
4. Marra, F., Vadlamudi, N.K. (2019). Efficacy and Safety of the Pneumococcal Conjugate-13 Valent Vaccine in Adults. Aging Dis. 1;10(2):404-418
5. Moberley, S., Holden, J., Tatham, D.P., Andrews, R.M. (2013). Vaccines for preventing pneumococcal infection in adults. Cochrane Database Sys Rev.1:Cd000422
6. National Pharmaceutical Regulatory Agency (NPRA) Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Received on September 5, 2019
7. Schmoele-Thoma, B., van Cleeff, M., Greenberg, R.N., Gurtman, A., Jones, T.R., Sundaraiyer, V., Gruber, W.C., Scott, D.A. (2019). Persistence of antibodies 1 year after sequential administration of the 13-valent pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine in adults. Hum Vaccin Immunother.15(3):575-583
8. Vadlamudi, N.K. et al (2019). Impact of the 13-valent pneumococcal conjugate vaccine among adults: A systematic review and meta-analysis. Clin Infect Dis; 69:34

Introduction

Poliomyelitis is an acute communicable disease caused by poliovirus and is spread mainly by the faecal-oral route. Of the 3 strains of wild poliovirus (type 1-3), wild poliovirus type 2 was eradicated in 1999 and no case of wild poliovirus type 3 has been reported since 2012. Only 2 countries in the world have never stopped transmission of polio (Pakistan and Afghanistan). These 2 countries continue to report cases of wild polio virus 1. Besides these 2 countries, circulating vaccine-derived polio virus (cVDPV) has been reported in 12 other countries in Africa, Eastern Mediterranean, South-East Asia and Western Pacific in 2020(www. polioeradication.org). In 2000, WHO certified Malaysia as polio-free. However, in December 2019, the Ministry of Health of Malaysia announced the country's first case of polio since 1992. Testing has confirmed that the virus strain of poliovirus that is genetically linked to the virus circulating in the Philippines.

On an average, about 1 in 75 adults who are infected, will develop paralytic poliomyelitis. The case fatality rate among paralytic cases is higher in adults (15-30%) compared to children (5-10%) predominantly due to bulbar involvement. Outbreaks of vaccine derived poliomyelitis occur in regions with low immunisation rates and poor sanitation. The low immunisation rates result in long term circulation of the vaccine-derived poliovirus in the population and thus allowing the virus to mutate and acquire back biologic properties similar to naturally occurring wild-type poliovirus. This results in vaccine-associated paralytic poliomyelitis (VAPP) among the unvaccinated.

Vaccines

Two types of poliovirus vaccines are currently available: oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV). Until 2015, over 90% of vaccine derived poliomyelitis were due to the type 2 component of OPV. In 2016 trivalent OPV was switched to bivalent OPV (type 2 polio virus was removed from the vaccine because it was eradicated in 1999) in the routine immunisation program in countries with high risk of transmission. In Malaysia OPV has been completely switched to IPV in the national immunisation program since 2010. IPV has mixture of inactivated, killed strains of all three poliovirus types.

Poliomyelitis

Vaccines Available in Malaysia

1. Oral Poliomyelitis Vaccine® (Attenuated polio vaccine)

Propharm (M) Sdn Bhd/PT Bio Farma, Indonesia

2. Imovax Polio® (Inactivated polio vaccine)

Sanofi Aventis (Malaysia) Sdn Bhd/Sanofi Pasteur, France

Note:

- IPV is also available in combination with DTP

Mode of Administration

- Inactivated poliovirus vaccine (IPV)

  » Adult dosage: 2 doses at an interval of two months. Booster to be given 8 to 12 months after the second injection.

  » Given into the deltoid muscle for intramuscular injection or the posterior aspect of the upper arm for subcutaneous injection.

Target Groups in Malaysia

- Travelers to polio-affected countries (refer to www.polioeradication.org for the list countries), who have previously received ≥3 doses of OPV or IPV, should be offered another dose of IPV as a once-only dose before departure.

- With the re-emergence of poliomyelitis in Sabah, Malaysians who wish to travel overseas to polio-free countries will need to check with the

respective embassies if they require an additional single dose of IPV/OPV 4 weeks to 12 months prior to international travel.

- Residents or long term visitors (i.e., four weeks) from polio-affected countries need to receive one dose of IPV/OPV 4 weeks to 12 months prior to international travel.

- Healthcare workers, including laboratory personnel, who may have come in contact with people with polio or poliovirus need to receive a booster dose of IPV and if at ongoing risk receive the vaccine every 10 years.

- Refugees from countries where wild polio is still endemic and have not completed the required 3 doses of poliomyelitis vaccination should receive their remaining doses. It does not matter how long it has been since the last dose.

- Unvaccinated adults whose children will be receiving oral poliovirus vaccine (for example, international adoptees or refugees) are higher risk individuals and may need 1 to 3 doses of IPV, depending on how many doses they have had in the past.
  - » Unvaccinated higher risk individuals should get three doses of IPV; two doses separated by 1 to 2 months, and a third dose 6 to 12 months after the second dose.
  - » Higher risk individuals who have had one or two doses of polio vaccine in the past should get the remaining one or two doses. It does not matter how long it has been since the earlier dose(s). Higher-risk adults who have had three or more doses of polio vaccine in the past may get a lifetime booster dose of IPV.

Contraindications and Adverse Effects

- In general, vaccination of pregnant women and immunocompromised persons should be avoided. However, if immediate protection is needed, IPV is recommended.

- Reported adverse events include transient minor local erythema (0.5–1%), induration (3–11%), and tenderness (14–29%)

- To date, the most frequently reported adverse event for OPV received by the National Pharmaceutical Regulatory Agency (NPRA) is fever. Cases of febrile seizure and convulsions had also been reported in children.

References

1. The Malaysian National Centre of Adverse Drug Reactions Database [Accessed: October 10, 2019].
2. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Updated September 5, 2019.
3. WHO (2016). Weekly Epidemiological Record, No 12, 25th March 2016; Polio vaccines; WHO position paper
4. WHO (2019). Statement of the 20th IHR emergency Committee; Regarding the International Spread of Poliovirus.

Introduction

Rabies is an acute progressive and almost always lethal zoonotic neurological infection. It is caused by rabies lyssa virus (formerly known as rabies virus) and family Rhabdoviridae. The enveloped RNA virus is ubiquitous worldwide except in Antarctica and some islands. Each year approximately 60,000 people die from rabies infection; more than 80% of the deaths occur in Asia and Africa. A further 15 million people receive post-exposure prophylaxis (PEP) against rabies every year.

Dogs are the most important animal reservoir for RABV. In rabies endemic areas virtually all human rabies cases are caused by infected dogs. RABV, which is found in saliva of an infected host, is predominantly transmitted through the bites, licks and scratches of rabid animals to new susceptible hosts. Direct person-to-person transmission of rabies has not been confirmed, except through organ transplantations that involved rabies-infected donors. The incubation period of the dreadful zoonotic infection is remarkably variable, although most of the infected humans become symptomatic between 2 and 3 months after exposure.

Human and animal rabies cases were first documented in Peninsular Malaysia in 1924 and 1925, respectively. Sporadic human cases have been reported in Peninsular Malaysia with the last case occurring in 1998. Between 2015 and 2018, several animal rabies clusters affecting the canine population were observed in several localities in Perlis, Kedah, Penang and Perak.

An on-going rabies outbreak affecting humans, dogs and cats was first detected in the southern region of Sarawak in July 2017. As of 9 September 2020, a total of 25 human rabies cases have been reported in Sarawak.

There is no effective antiviral treatment once the rabies symptoms appear. Whilst the case fatality rate of human rabies exceeds 99% for those previously unvaccinated and did not receive any PEP, rabies is preventable through the use of safe, highly effective and well-tolerated modern, concentrated, purified cell culture and embryonated egg-based rabies vaccines (CCEEVs).

WHO Recommends 2 Key Human Immunisation Strategies for the Prevention of RABV Infection:

1. After exposure (Post-Exposure Prophylaxis, PEP) (Refer to Table 14.1 on page 145):

- It involves the institution of three timely life-saving steps following a potential exposure to RABV. The 3 steps encompass prompt and meticulous wound care (viz. thorough washing and irrigation of wounds, scratches or RABV-exposure sites with running water and soap or detergent for at least 15 minutes followed by wound dressing with iodine, alcohol or anti-septic), administration of CCEEVs, and local wound infiltration with rabies immunoglobulins (RIG) or monoclonal antibody (if indicated).
- WHO recommends PEP for category II and III exposure, according to the following definitions
  - » **Category I (no exposure)**: Touching or feeding animals, licks on intact skin
  - » **Category II (exposure)**: Nibbling of uncovered skin, minor scratches or abrasions without bleeding
  - » **Category III (severe exposure)**: Single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, exposure to bat bites or scratches

Figure 14.1
Post-exposure Prophylaxis (PEP) Based on Category of Exposure and Rabies-Immune Status (Adapted from WHO Position Paper April 2018)

	Category I exposure	Category II exposure	Category III Exposure
Immunologically naive individuals of all age groups	Wash exposed skin surfaces No PEP required	Wound washing and immediate vaccination: • 2-sites ID on days 0, 3 and 7# **OR** • 1-site IM on days 0, 3, 7 and 14 to 28$ RIG administration is not indicated	Wound washing and immediate vaccination: • 2-sites ID on days 0, 3 and 7# **OR** • 1-site IM on days 0, 3, 7 and 14 to 28$ RIG administration is recommended
Previously immunised* individuals of all age groups (<3 months from the last date of completed vaccination series – either PEP or PrEP)	Wash exposed skin surfaces No PEP required	Wash exposed skin surfaces No PEP required	Wash exposed skin surfaces No PEP required

Rabies

	Category I exposure	Category II exposure	Category III Exposure
Previously immunised* individuals of all age groups (>3 months from the last date of completed vaccination series – either PEP or PrEP)	Wash exposed skin surfaces No PEP required	Wound washing and immediate vaccination: • 1-site ID on days 0 and 3; **OR** • at 1-site IM on days 0 and 3; RIG is not indicated.	Wound washing and immediate vaccination: • 1-site ID on days 0 and 3; **OR** • at 1-site IM on days 0 and 3; RIG is not indicated.

Footnote:

ID: intradermal injection; IM: intramuscular injection; RIG: rabies immunoglobulins.
[#] One-week, 2-site ID regimen (Institut Pasteur du Cambodge regimen); duration of entire PEP course: 7 days.
[$] Two-week, 1-site IM regimen (4-dose modified Essen regimen); duration of entire PEP course: between 14 and 28 days.

***Individuals with documented evidence of previous PrEP, or at least 2 previous administrations of rabies vaccine as PEP, are considered previously immunised and benefit from an abridged PEP without RIG in case of exposure.**

In the case of HIV-infected individuals who are not on ART or on ART but CD4 count <200cells/mm^3 and other potentially immunocompromised individuals, a full course of rabies vaccine with RIG is indicated, even if they are previously immunised. All immunocompromised cases that need PEP should be referred to infectious disease specialist.

2. Before exposure (Pre-Exposure Prophylaxis, PrEP)

- It aims to prime the immune system before there is an exposure to RABV so that a strong anamnestic immune response could be elicited effectively, even many years after, when there is a re-exposure to RABV and following post-exposure booster.

- The schedules are:

  » 2-site ID vaccine administered on Day 0 and 7

  » 1-site IM vaccine administration on Day 0 and 7

  In the case of immunocompromised individuals, a 3-visit regimen consists of either 2-site ID or 1-site IM vaccine administration on Day 0, 7 and between Days 21-28 should be used. They should be managed with full PEP in the event of potential RABV exposure.

  HIV-infected individuals receiving antiretroviral therapy with CD4 count > 200cells/μL are considered not to be immunocompromised; they have been shown to respond to rabies and other vaccines in the same way as healthy individuals. Nonetheless, in the event of exposure, a complete PEP course, including RIG, is recommended.

- PrEP is recommended for individuals at high risk of RABV exposure:

  a. Individuals at occupational risk; such as those involved in rabies research, biologics production and diagnostic laboratories, those involved in animal disease control and wildlife management at settings where rabies may be enzootic, those involved in bat handling or caving activities that may have direct contact with bats, those working in remote rabies-enzootic areas where timely and adequate access to PEP is uncertain e.g. dog vaccination campaign workers, peace keeping, military or religious missions.

  b. Travelers who may be at risk of RABV exposure.

c. Populations living in highly endemic areas, where annual dog bite incidence is >5%, with limited access to timely and adequate PEP

Vaccines available in Malaysia

1. Verorab® (inactivated purified vero cell, PVRV)

- Sanofi-Aventis (Malaysia) Sdn Bhd/Sanofi Pasteur, France

2. Rabipur® (inactivated, purified chick embryo cell, PCEC)

- Glaxo-Smith-kline Pharmaceutical Sdn Bhd/Chiron Behring Vaccine Private Ltd, India

Mode of Administration of Rabies Vaccines

1. ID route
   - It is the preferred administration because it is cost, dose and time saving when compared to the IM route
   - Use insulin syringe (30G X 5/16", 0.3mm X 8mm) and needle for ID administration
   - An ID dose is 0.1 mL of vaccine
   - Injection site: deltoid, anterolateral thigh or suprascapular regions

2. IM route
   - An IM dose is the entire content of the vial i,e. either 0.5 or 1.0 mL depending on the vaccine brand.
   - Injection site: deltoid region for adults and children aged >2 years. Rabies vaccine should not be administered IM in the gluteal area.

Additional Notes On Rabies Vaccine Administration

i. If any doses are delayed, vaccination should be resumed, NOT restarted.

ii. A change in the administration route or vaccine product during a PEP course is acceptable if such a change is unavoidable.

Rabies Immunoglobulin (RIG) and Rabies Monoclonal Antibody (mAb) Available In Malaysia#

1. RIG types
   - There are 2 types of RIG available for passive immunisation: human rabies immunoglobulin (hRIG) and equine rabies immunoglobulin (eRIG)
   - Both hRIG and eRIG are equally effective and safe.
   - There are a number of RIG products and manufacturers globally but none has received WHO pre-qualification.

2. Rabies monoclonal antibody
   - There is only a single mAb product against RABV (Rabishield®, Serum Institute of India) licensed for use in human to date.

RIG and Mab are not readily available in Malaysia but may be imported upon special request from the Ministry of Health. The import permits of the biologics may be applied by using Borang Bpf/213-1: Borang Permohonan Mengimport/ Mengilang Keluaran Tidak Berdaftar Bagi Tujuan Merawat Penyakit Yang Mengancam Nyawa (http://www.pharmacy.gov.my/v2/sites/default/files/document-upload/bpf213-1_1.pdf). Further detailed information may be obtained from Application Guidance Notes (http://www.pharmacy.gov.my/v2/sites/default/files/ document-upload/panduan-syarat-mengisi-borang-lampiran-bpf213-1-pindaan-1.pdf). The completed forms should be submitted to:

Pengarah Kanan Perkhidmatan Farmasi,
Bahagian Perkhidmatan Farmasi,
Kementerian Kesihatan Malaysia,
Lot 36, Jalan Universiti,
46350 Petaling Jaya,
(U/P: Cawangan Perundangan, Bahagian Penguatkuasaan Farmasi)
No. Tel: 03-78413200
No. Faks: 03-79682251

Mode of Administration of RIG and Rabies mAb

1. The principle and rationale

   - RIG neutralises RABV in-situ within a few hours of its infiltration into and around the local wound before the adaptive immune system can respond to the rabies vaccine by the production of vaccine-induced neutralising antibodies.

   - The rabies biologics (RIG and mAB) should be administered only once, preferably at, or as soon as possible after, the initiation of PEP. It is no longer indicated beyond Day 7 following the first rabies vaccine dose as active humoral antibody response to rabies vaccine has already started. Administration of RIG beyond this time may result in interference in adaptive immune response to active rabies immunisation.

   - Regardless of the size, all wounds should be identified and infiltrated with RIG.

- Suturing of wounds should be delayed for 6-8 hours after RIG infiltration, or if unavoidable, sutures should be loose to allow optimal RIG diffusion around the wound.

- Modern purification techniques have made the current eRIGs highly purified and refined preparations. The risk of serious adverse reaction is minimal. Skin testing before eRIG administration is not recommended because it does not predict the occurrence of adverse effects.

2. Dosage of RIG and mAb

» The maximum dose of

♦ hRIG: 20 iu/kg body weight

♦ eRIG: 40 iu/kg body weight

♦ mAb (Rabishield®): 3.33 iu/kg body weight

- There is no minimum dose of RIG. The rabies biologics should be infiltrated as much as possible into and around the wound only. The remainder amount of the calculated rabies biologics does not need to be injected intramuscularly at a distance from the wound. Instead it may be fractionated in aseptic manner into smaller, individual syringes and stored at 2-8°C for other patients' use. Unused rabies biologics should be discarded at the end of the clinic day.

- Caution should be practiced to avoid the occurrence of compartment syndrome when a large volume of rabies biologics is injected into anatomical restricted areas e.g. finger and ear pinna.

- In the event that there are large & multiple bite wounds, rabies biologics may be diluted with 0.9% normal saline (up to 2-3 times of the calculated volume) so that all wounds could be adequately infiltrated.

- Rabies vaccination should never be withheld, regardless of the availability of RIG or mAB. The importance of prompt meticulous wound care, together with immediate administration of the first vaccine dose, and followed by a complete course of rabies vaccine is highly effective in prevention of human rabies and could be not overemphasized.

- If RIG or mAb is of limited supply, its allocation should be prioritised for RABV-exposed patients based on the following criteria:

  a. the biting animal is a laboratory-confirmed or probable rabies case,

  b. multiple bites,

  c. deep wounds,

  d. bites to highly innervated body parts (e.g. head, neck and hands),

  e. severe immunodeficiency,

  f. bites, scratches or exposures of mucous membranes caused by a bat.

Co-administration with Other Vaccines

Rabies vaccines can be co-administered with other inactivated and live vaccines, using separate syringes and different injection sites.

Contraindications and Adverse Effects

1. Individuals with a history of severe hypersensitivity to any of the components or to excipients listed by the vaccine manufacturer should receive an alternative rabies vaccine product for PrEP.

2. There is no contraindication to PEP and PrEP, including for infants, pregnant and lactating women, HIV-infected and other immunocompromised individuals and those receiving with chloroquine or hydroxychloroquine treatment. Where possible, PrEP should be completed before chloroquine or hydroxychloroquine treatment is initiated.

3. Reported adverse events include transient minor local erythema (0.5-1%), induration (3-11%), and tenderness (14-29%).

To date, the most frequently reported adverse event for rabies received by the National Pharmaceutical Regulatory Agency (NPRA) is pruritus, headache and fever.

Unlike nerve-tissue derived rabies vaccines that can induce severe adverse reactions and is no longer recommended by WHO, CCEEVs are safe and well-tolerated. Minor and transient local adverse reaction such as erythema, pain and/or swelling may occur at the site of injection in 35-45% of recipients. Mild systemic adverse events such as transient fever, headache, dizziness and gastrointestinal symptoms, have been reported in 5–15% of recipients.

Target Groups in Malaysia

- Travelers to rabies endemic areas
- Veterinarians and animal handlers

Evidence for Effectiveness

Modern CCEEVs are highly immunogenic. They induce a prompt and strong vaccine-induced neutralising antibody response to the G protein of RABV. A minimum serum antibody concentration of 0.5 IU/mL is widely used and recommended by WHO as a measure of adequate seroconversion following vaccination. The antibody titer is reached by day 7–14 of a PEP regimen, with

or without simultaneous administration of RIG in most individuals, regardless of their age or nutritional status.

Whilst PEP using modern CCEEVs is known to be highly effective, it does not necessarily confer 100% protection against the development of human rabies infection. Delay in seeking PEP, inadequate wound care, unnoticed wounds, direct neural inoculation, use of ineffective rabies vaccine, improper vaccine administration (e.g. subcutaneous injection) or non-adherence to vaccination schedule and poor quality vaccine (non-WHO prequalified or cold-chain quality issue) are several important reasons for PEP failure in humans.

References

1. Abela-Ridder, D. (2018). WHO Expert Consultation on Rabies: WHO TRS N°1012.
2. Begeman, L., Geurtsvankessel, C., Finke, S., Freuling, C. M., Koopmans, M., Müller, T., . . . Kuiken, T. (2018). Comparative pathogenesis of rabies in bats and carnivores, and implications for spillover to humans. The Lancet Infectious Diseases, 18(4). doi:10.1016/s1473-3099(17)30574-1
3. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Updated September 5, 2019
4. The Malaysian National Centre of Adverse Drug Reactions Database. Accessed October 10, 2019
5. World Health Organization Rabies vaccines: WHO position paper, April 2018 – Recommendations. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.06.061
6. World Health Organization Rabies vaccines: WHO position paper – April 2018 Weekly epidemiological record No 16, 2018, 93, 201–220

Introduction

Typhoid is caused by *Salmonella enterica* subspecies *enterica* serovar Typhi (previously *Salmonella typhi*). Humans are the only reservoir of *S.* Typhi. Transmission is via the ingestion of faecally contaminated food or water. In Malaysia, typhoid is among the food and water borne diseases besides cholera, food poisoning, hepatitis A and dysentery which are notifiable under the Prevention and Control of Infectious Diseases Act 342.

A classical case of typhoid fever presents with fever, headache and constipation (typically diarrhoea in young children). Clinical findings include abdominal tenderness, relative bradycardia and splenomegaly. Complications occur in 10% of cases which may result in intestinal perforation, gastrointestinal haemorrhage and encephalopathy. Up to 5% of patients with typhoid fever may become chronic carriers and may continue to shed (through the patients faeces) the organisms for more than 1 year. Carriers serve as reservoirs in endemic areas and are of considerable public health importance, particularly if they work in the food industry.

Typhoid is endemic in Malaysia with an average incidence rate of 0.76 per 100 000 population reported annually in recent years (2014-2019). The incidence rate was 0.53 per 100,000 population in 2018.

Typhoid is also regarded as a travel-related disease with a considerably higher risk following travel to the Indian subcontinent, most Southeast Asian countries and several South Pacific nations.

The importance of vaccination for typhoid is heightened by increasing resistance of *S.* Typhi to antimicrobial agents, including fluoroquinolones, in many parts of the world.

Typhoid

Vaccines

- There are 2 types of typhoid vaccines which are available in oral or parenteral formulation.

1. The oral vaccine contains the attenuated non-pathogenic *S.* Typhi strain Ty21a which is derived by chemical attenuation of a wild-type strain. The vaccine lacks the Vi capsular polysaccharide antigen; an important virulence factor of *S.* Typhi.

2. The parenteral vaccine contains purified Vi capsular polysaccharide of *S.* Typhi (Ty 2 strain). The purified polysaccharide capsule is diluted in isotonic buffer solution which contains phenol as preservative.

Vaccines Available in Malaysia

1. Typhim Vi® (Purified Vi capsular polysaccharide, single or 20 doses)
Sanofi Aventis (M) Sdn Bhd/Sanofi Pasteur, France
2. Vivotif Oral® (Oral live attenuated Ty21a typhoid)
Propharm (M) Sdn Bhd/PaxVax Berna, Switzerland
3. Typherix® (Purified Vi capsular polysaccharide)
GlaxoSmithKline Pharmaceutical Sdn Bhd/GlaxoSmithKline Biologicals, Belgium

Mode of Administration

1. **Oral live attenuated vaccine**

   - It is available in a pack of 3 capsules. The vaccine schedule is as follow: 1 capsule on each of days 1, 3 and 5 to be taken 1 hour before meals with cold or lukewarm water (not more than 37°C). The capsule must be swallowed whole and not chewed.

2. **Parenteral Vi polysaccharide vaccine**

   - The monovalent typhoid vaccine is given as a single dose of 0.5 ml via IM injection.

Typhoid vaccines lose effectiveness over time. The injectable vaccine requires a booster every 2 years and the oral vaccine requires a booster every 5 years.

Co-administration with Other Vaccines

- Oral typhoid vaccine can be administered simultaneously as any of the live parenteral vaccines and immunoglobulins. It is recommended that the last dose of vaccination be given at least 3 days before starting antibiotics or anti-malarial prophylaxis as these drugs may interfere with the protective effect of the live attenuated vaccine.

- Parenteral Vi polysaccharide typhoid vaccine can be given with other vaccines indicated for travel.

Contraindications and Adverse Effects

- The only absolute contraindication to typhoid vaccine is anaphylaxis reaction after a previous dose to any typhoid vaccine or to any component of the vaccine. Both types of vaccines are associated with very few adverse reactions.

- Oral live attenuated vaccine should not be administered to pregnant women, immunocompromised persons and persons taking antibiotics. Adverse reactions include abdominal discomfort, diarrhoea, nausea and vomiting.

- Parenteral Vi polysaccharide vaccine may cause adverse effects such as local reactions at the injection site consisting pain, redness and swelling. Fever and headache may be present.

- To date, the reported adverse events for typhoid vaccine received by the National Adverse Drug Reactions Monitoring Centre (NPRA) are erythema, fever and diarrhoea.

Target Groups in Malaysia

- Food handlers and vendors.
- Travelers to areas in which there is a recognised risk of exposure to S. Typhi.
  - » The parenteral vaccine should be given at least 2 weeks before travel
  - » For the oral vaccine, all doses should be completed at least 1 week before travel
- Risk is greatest for travelers to developing countries where food hygiene may be suboptimal and drinking water may not be adequately treated. Travelers should be cautioned that typhoid vaccination is not a substitute for careful selection of food and drink as the efficacy is only about 60-70%.
- Persons with close contact (household contact) to a documented *S.* Typhi carrier.

Implications for Healthcare Workers (HCWs)

- Typhoid vaccines should be employed as part of comprehensive control strategies in areas where the disease is endemic. Working in a health care

setting is not indicated as a factor for increased risk. There is currently no recommendation regarding HCWs

Evidence for Effectiveness

- Clinical trials with different formulations of the oral vaccine Ty21a strain in a variety of schedules, have been undertaken in countries (Egypt, Chile and Indonesia) where typhoid is endemic. These have documented varying degrees of protection against the disease. Parenteral Vi polysaccharide vaccines have also been used in clinical trials in endemic regions (Nepal, South Africa, China), indicating moderate protection against typhoid fever.

- In controlled trials conducted among schoolchildren in Chile, 3 doses of the Ty21a vaccine in enteric-coated capsules administered on alternate days reduced laboratory-confirmed infection by 66% over a period of 5 years.

- A meta-analysis comprising 17 studies and nearly 2,000,000 people showed that for the whole cell vaccines, single dose regimens provide significant protection for the first 2 years. Two dose regimens provided significant protection for 5 years. For the Ty21a vaccine, both the 2-and 3-dose regimens provided statistically significant protection for 2 years. The 3-dose regimen provided protection in the 3rd and 4th years, but protection was not statistically significant in the 5th year. The Vi polysaccharide vaccine provided protection for 2 years, but the protection in the 3rd year was not significant.

References

1. Bhan, M.K., Bahl, R., Bhatnagar, S. (2005). Typhoid and paratyphoid fever. The Lancet, 366, 749-62
2. Centers for Disease Control and Prevention (CDC). (2011). Recommendation of the Advisory Committee on Immunisation Practices (ACIP). Immunisation of Health-Care Personnel. MMWR, 60(7). https://www.cdc.gov/mmwr/pdf/rr/rr6007.pdf
3. Centers for Disease Control and Prevention (CDC.) (2015). Advisory Committee on Immunization Practices. Updated Recommendations for the Use of Typhoid Vaccine. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a4.htm
4. Engels, E.A & Lau, J.(2002). Vaccines for preventing typhoid fever. Cochrane Infectious Diseases Group. Cochrane Database Syst Rev. Issue 4
5. Ferreccio, C,. Levine, M. M., Rodriguez, H., Contreras, R. (1989). Chilean Typhoid Committee. Comparative efficacy of two, three, or four doses of TY21a live oral typhoid vaccine in enteric-coated capsules: A field trial in an endemic area. J Infect Dis, 159, 766-9
6. Malaysian National Centre of Adverse Drug Reactions database. https://npra.gov.my
7. Ministry of Health Malaysia. (2019). National Pharmaceutical Regulatory Agency (NPRA). Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah.
8. Ministry of Health of Malaysia (MOH). (2011). Annual report. http://www.moh.gov.my
9. Ministry of Health of Malaysia (MOH). (2014-2019). Health facts: Incidence rate and mortality rate of communicable diseases.
10. Summary of WHO Position Paper. (2019). Immunisation of healthcare workers
11. WHO Position Paper (2008). Typhoid vaccine. Weekly Epidemiol Rec, 6(83), 49-60. https://www.who.int/wer

Varicella

Introduction

Varicella or chickenpox presents as fever, vesicular rash, itching and tiredness. It is caused by the varicella-zoster virus (VZV), also known as human herpesvirus 3 (HHV-3). It undergoes latency after primary infection and later reactivates as herpes zoster (HZ, shingles). Seroconversion in tropical countries occurs at a later age than in temperate countries making varicella common in adolescents and adults. The spectrum of varicella varies from mild in some people, to significant morbidity and some mortality in previously healthy persons. The live attenuated varicella vaccine (Oka strain) was developed by Takahashi in 1974, and it was registered in Japan in 1986. Since then monovalent varicella vaccines have been made available throughout the world for the prevention of infection in healthy children, adolescents and adults. Combination vaccines for the prevention of measles, mumps, rubella, and varicella became available in 2005.

VZV is transmitted by the airborne route or direct contact with vesicular fluid. It is highly contagious with secondary attack rates in susceptible household contacts ranging from 61-100%. VZV can also be transmitted to susceptible persons from patients with HZ. Studies suggest that the risk of viral transmission is considerably less from HZ than from varicella.

In an immunocompetent person, malaise and fever occur 1 or 2 days before the onset of rash. Patients with varicella typically have a generalised vesicular rash concentrated on the head and trunk. The rash appears in crops; each crop usually progresses within 24 hours from macules to papules, vesicles, pustules and finally crusts. New lesions occur in crops over the next few days, with various stages of healing. The lesions are pruritic and may cause scars. Adults with varicella have significantly higher morbidity than varicella in children.

VZV has the capacity to persist in the body after primary infection as latent infection in sensory nerve ganglia. VZV specific cell mediated immunity (CMI) plays import role in limiting reactivation of latent VZV. Decline in CMI leads to reactivation of VZV and herpes zoster.

Varicella

The two-dose varicella vaccination programme has lowered the varicella incidence, outbreaks and hospitalisations, and has squashed concerns that routine childhood vaccination could lead to increase in HZ.

Varicella may be more severe in pregnant women (especially in the last trimester). Foetal morbidity is increased in maternal varicella. Varicella during pregnancy may damage the foetal central nervous system (CNS), resulting in permanent scarring of the skin, aplasia of extremities, chorioretinitis, microphthalmia, optic atrophy, cataract, Horner's syndrome, blindness, mental retardation, foetal demise, and a high incidence of zoster and death in infancy. This constellation of problems in infants whose mothers had varicella in pregnancy is clinically diagnostic of the congenital varicella syndrome.

Maternal varicella that develops within 5 days before or 2 days after delivery, is potentially most serious for the newborn. Maternal antibodies to VZV may not have been formed or crossed the placenta and VZV may infect the baby before or after delivery. Immaturity of the infant's cellular immunity, put the infant at risk for severe varicella. The infected infant may develop haemorrhagic skin lesions and primary varicella pneumonia. Severe varicella can usually be avoided with prophylactic administration of passive immunisation and acyclovir (ACV) therapy. Vaccination of women before pregnancy is the preferable strategy.

Vaccines Available in Malaysia

1. Varilrix® (Live attenuated Oka strain of varicella-zoster virus)
GlaxoSmithKline Pharmaceuticals Sdn Bhd/GlaxoSmithKline Biologicals, Belgium
2. Varivax® (Live attenuated Oka/Merck strain of varicella-zoster virus)
Merck Sharp & Dohme (M) Sdn Bhd/ Merck Sharp & Dohme Vaccine, US contains processed porcine gelatine

Mode of Administration

- The vaccine is administered subcutaneously. Although data on the intramuscular route are limited, it too seems to be safe and effective. All manufactured varicella vaccines are lyophilised; both refrigerator-stable and frozen vaccine formulations are available.

- Persons 13 years and older without evidence of immunity should receive 2 doses of monovalent varicella vaccine, 4-8 weeks apart. If an interval longer than 8 weeks elapses after the 1st dose, the 2nd dose can be administered without restarting the schedule.

- Monovalent vaccines are to be used in adults as **MMRV vaccine is approved for use in children 12 months through 12 years of age**.

Contraindications and Adverse Effects

- Although no infants with congenital varicella syndrome secondary to vaccine type virus have been reported, vaccination in pregnancy is contraindicated.

- To date, the reported adverse events for varicella vaccine received by the National Pharmaceutical Regulatory Agency (NPRA) are varicella-like rashes occurring 7-23 days post vaccination and fever.

Varicella-containing vaccine should be given at least 2 weeks before the administration of blood products. In subjects who have received immune globulins or a blood transfusion, immunisation should be delayed for at least three months because of the likelihood of vaccine failure due to passively acquired varicella antibodies.

Varicella

Target Groups in Malaysia

- Adults who have no history of previous varicella infection. Because varicella infection is more severe among adolescents and adults, vaccination is important for them. Monovalent vaccines are to be used in adults as **MMRV vaccine is approved for children 12 months through 12 years of age**.

- Vaccinating adult groups at high risk of exposure/transmission or close contact with persons at high risk of severe varicella should be a priority. These groups include students in schools, colleges and universities, international travelers, and healthcare workers.

- To prevent congenital varicella, women who do not have previous natural infection or vaccination are advised to receive varicella vaccination before they start a family and they should avoid pregnancy for 3 months following vaccination. If already pregnant, they should be vaccinated postnatally.

Implications for Healthcare Workers (HCWs)

- Nosocomial transmission of VZV is a well-recognised medical problem. Because of their high risk of exposure to varicella or HZ and close contact with persons at high risk for serious complications, healthcare workers should be routinely vaccinated with two doses of varicella vaccine unless they have other evidence of immunity. Serologic testing after vaccination is not recommended unless a sensitive and specific test can be used. Available commercial assays are not sensitive enough to detect low levels of antibody after vaccination.

- Varicella vaccine is recommended for post-exposure vaccination, for outbreak control, and for certain groups in whom there is adequate data on vaccine safety and immunogenicity or efficacy.

Evidence for Effectiveness

- The National Institute for Allergy and Infectious Diseases (NIAID) conducted a collaborative study on 350 healthy adults in 1980-1990 in which most of them were given 2 doses. Their fluorescent antibody to membrane antigen (FAMA) seroconversion rate was 82 % after one dose and 90% after two doses. Thirteen years after vaccination, 60-90% were positive by FAMA or latex agglutination antibody tests. In subsequent follow-up studies of a subset of these vaccine recipients (120 healthcare workers), 31% lost detectable FAMA antibodies, on average 8 years later. Twelve (10%) developed varicella; all had mild infections despite loss of detectable VZV antibodies.

- In a multicentre study using Oka/Merck in 539 adolescents and adults, 75% seroconverted after first dose and 99% after second dose. A second multicentre Oka/Merck study involving 142 adolescents and adults showed 94% seroconversion after first dose and 99% after second dose.

References

1. Gershon, A.A., Marin, M. J. F., Seward, J.F. (2018) Varicella vaccine. In Plotkin S.A., Orenstein W.A., Offit, P.A., Edwards K.M.(Eds) Vaccines. (7th Edition) Saunders Elsevier.
2. MSD. Varivax® Refrigerated Local Product Circular
3. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Updated 5 September, 2019
4. The Malaysian National Centre of Adverse Drug Reactions Database [Accessed: 10 October, 2019]
5. Wang, L., Zhu, L , Zhu, H. (2016) Efficacy of varicella vaccination: an update for the clinicians. Ther Adv Vaccines,4,20-31

Yellow Fever

Introduction

Yellow fever (YF) is an acute viral haemorrhagic disease, caused by an arbovirus of the genus Flavivirus and family Flaviviridae. It is transmitted by the bite of female mosquitoes (several species of the *Haemogogus* and *Aedes* including *Aedes aegypti*). Primates and several species of mosquitoes are the only hosts. YF is endemic in the sylvatic setting in sub-Saharan Africa and the tropical regions of South America, but not in Asia. In the jungle form, YF is spread from mosquitoes to monkeys and also to humans (zoonosis). Urban YF may cause large outbreaks in cities and suburbs, in which infected mosquitoes transmit the virus to human. Outbreaks occur periodically in Africa and sporadically in South America. The presence of Aedes mosquito vector in Asia may contribute to its potential occurrence. Malaysia is vulnerable to YF transmission.

The incubation period is 2-5 days. Some cases are asymptomatic but most lead to an acute illness characterised by two phases. The infection is characterised by flu-like symptoms, including fever, headache, muscle pain, backache, anorexia, nausea, and vomiting, often with bradycardia. About 15% will develop a second phase with severe symptoms within 48 hours, including vomiting, abdominal pain, jaundice, haemorrhage, shock, and multiple organ failure. Haemorrhagic manifestations include epistaxis, gingival bleeding, haematemesis, melaena, and liver and renal failure. The acute form of the disease is viral haemorrhagic fever which can lead to death within 10-14 days in 50% of cases in non-indigenous individuals (namely travelers) and during epidemic. Among the indigenous populations in endemic areas, fatality is around 5%. There is no specific treatment for yellow fever. Patients are advised plenty of rest, fluids and regular painkillers (e.g. paracetamol or ibuprofen) for symptomatic relief of fever or aches.

WHO recommends that all endemic countries should introduce YF vaccine into their routine immunisation programmes. Preventive mass vaccination campaigns are recommended for inhabitants of areas at risk of YF where there is low vaccination coverage. Vaccination is recommended to be given to everyone aged ≥ 9 months, in any area with reported cases. Reported cases of human disease is the principal indicator of disease risk, but may

be absent due to a high level of immunity in population, or not detected due to lack of surveillance. Travelers to endemic countries with risk of YF transmission of Africa, Central and South America are at risk. Some countries require proof of YF vaccination for entry. When traveling to low risk YF areas, travelers should take adequate measures to prevent mosquito bites during the daytime.

There are 3 reasons for YF vaccination:

- To provide individual protection and reduces the risks of infection for those living in epidemic and endemic YF areas.
- To protect individual travelers who may be exposed to YF infection.
- To prevent the spread of YF by viraemic travelers on an international scale.

This is to protect countries from the risk of importing or further spreading YF virus by establishing entry requirements on YF vaccination for travelers. The countries that require proof of vaccination are those where the disease may or may not occur, and where the mosquito vector and potential non-human primate hosts of YF are present.

Following an update by the World Health Assembly in 2014, WHO announced that as of 11 July 2016, existing and new YF vaccination certificates are valid for life starting 10 days after vaccination. Countries can no longer require travelers to show proof of re-vaccination or a booster dose as a condition of entry.

Vaccines

YF vaccine has been available for more than 80 years. It is a live attenuated freeze dried preparation of the 17D strain of yellow fever virus. A single dose correctly given, provides lifelong protection in nearly 100% of recipients. It is a safe and effective vaccine, which is recommended for people aged 9 months or older and who are traveling to or living in areas at risk for YF virus in Africa and South America. YF vaccine may be required for entry into certain countries.

Yellow Fever

Vaccines Available in Malaysia

1. Stamaril (live attenuated, 17D-204 strain vaccine)
Sanofi Aventis (M) Sdn Bhd/Sanofi Pasteur, France

Certification of vaccination can be obtained from the Virology Division, Infectious Diseases Research Centre, The Institute for Medical Research Kuala Lumpur and various other designated centres in the country. Details on Yellow Fever Vaccination Centres in Malaysia can be obtained from the Ministry of Health website:

http://www.moh.gov.my/moh/images/gallery/Garispanduan/Yellow_Fever_Vaccination_Centre_in_Malaysia_new%20updated.pdf

Mode of Administration

- The vaccine should be given by subcutaneous injection as a single 0.5mL dose.
- Children aged 9 months and older: a single dose of 0.5 ml of the reconstituted vaccine.
- Children from 6 to 9 months of age: vaccination against yellow fever is not recommended in children aged from 6 months up to 9 months except in specific circumstances and in accordance with available official recommendations, in which case the dose is the same as in children aged 9 months and older.
- Children under 6 months of age: Stamaril is contraindicated in children less than 6 months of age.
- YF vaccine may be administered simultaneously with other vaccines.

Contraindications and Adverse Effects

- The vaccine is contraindicated in:
  - » Immunocompromised or on immunosuppressive or immunomodulatory therapies
  - » Individuals allergic to eggs.
  - » Children before 6 months of age.
  - » HIV patients with CD4 <200 /mm^3 or symptomatic HIV infection.
  - » Persons with thymus disorders, malignant neoplasms
  - » Transplant recipients

- Pregnant and lactating mothers: noting that YF is a live vaccine, a risk-benefit assessment should be undertaken for all pregnant and lactating women. In areas where YF is endemic, or during outbreaks, the benefits of YF vaccination are likely to far outweigh the risk of potential transmission of vaccine virus to the fetus or infant.

- If vaccination is contraindicated for medical reasons, an exemption letter or waiver should be issued to the traveler. However, acceptance or acknowledgment of such a letter is at the discretion of the destination country, and entry might be denied.

- The adverse effects include local site reactions and systemic reactions such as headache, myalgia and pyrexia.

- To date, the reported adverse events for YF vaccines received by the National Pharmaceutical Regulatory Agency (NPRA) include fever, headache and abdominal pain.

Target Groups in Malaysia

- Yellow fever vaccination is recommended for all travelers ≥9 months old in areas where there is evidence of persistent or periodic yellow fever virus transmission.

Yellow Fever

- Some categories of travelers should consider vaccination depending on risk assessment of YF infection at their destination and a country's entry requirement:

  » Children between the ages of 6 to 8 months

  » Persons over 60 years

  » HIV patients with CD4 ≥200 /mm^3

  » Pregnant or breastfeeding women.

  » Laboratory personnel who may be exposed to the virulent virus.

Recommendations

- YF vaccination is recommended for persons travelling or living in areas in which YF infections occur.
- Vaccination is mandatory for all persons travelling from or to countries endemic to YF (refer to the WHO website for the current list of countries www.who.int/ith).
- A single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease. A booster dose is not necessary, but may still be required by some countries. Adjustments of the provisions for the duration of validity of certificates under the IHR are ongoing.
- A YF vaccination certificate is required from all visitors (Malaysians and foreigners) coming from or going to/through countries with risk of YF transmission (As stated in International Health Regulations 2005 and Prevention and Control of Infectious Disease Act 1988).
- YF vaccination is also required for travelers having transited more than 12 hours through the airport of a country with risk of YF transmission.

- Travelers or delegates without a valid YF vaccination or prophylaxis certificate shall be quarantined upon arrival in Malaysia for a period not exceeding 6 days.

- Travelers are advised to take the vaccination at least 10 days before the date of departure to countries with risk of YF transmission for protection against infection. International certificate of vaccination or prophylaxis becomes valid 10 days after the date of vaccination.

- The International Certificate of Vaccination or Prophylaxis, International Health Regulations (2005) is available at WHO website,

  https://www.who.int/ihr/IVC200_06_26.pdf

- To carry the international certificate of vaccination during travel for health check.

- To get the vaccination at the Approved Yellow Fever vaccinating centres in Malaysia.

- To report to Entry Point Health Office on arrival in Malaysia for health check.

- YF vaccination is generally not recommended in areas where there is low potential for YF virus exposure (no human YF cases ever reported and evidence to suggest only low levels of YF virus transmission in the past). However, vaccination might be considered for travelers to these areas, who are at increased risk of exposure to mosquitoes or unable to avoid mosquito bites.

- When considering vaccination, a risk-benefit assessment should be undertaken; the risk of being infected with YF virus, country entry requirements, as well as individual risk factors for serious vaccine-associated adverse events such as age and immune status.

Yellow Fever

HCW

- Healthcare workers are not at an increased risk. There is currently no specific recommendation regarding HCWs.

Evidence for Effectiveness

- Close to 100% seroconversion rates have been shown with YF vaccines. Factors that have been associated with failure to respond immunologically to YF vaccine include HIV infection, pregnancy, and malnutrition.

- A single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease; a booster dose is not necessary except in select cases.

References

1. Centers for Disease Control and Prevention, US. Yellow Fever Travel Information. Available at https://wwwnc.cdc.gov/travel/page/yellow-feverinformation. Accessed March 2019.
2. David L. Heymann. (2004). Control of Communicable Diseases Manual, 18th Edition. Washington DC, USA: American Public Health Association.
3. Lang, J., Zuckerman, J., Clarke, P., Barrett, P., Kirkpatrick, C., & Blondeau, C. (1999). Comparison of the immunogenicity and safety of two 17D yellow fever vaccines. The American Journal of Tropical Medicine and Hygiene, 60(6), 1045–1050. https://doi.org/10.4269/ajtmh.1999.60.1045
4. Malaysia Required Vaccinations: Yellow Fever. Available at https://www.iamat.org/country/malaysia/risk/ yellow-fever. Accessed March 2019.
5. Meeting of the Strategic Advisory Group of Experts on immunization, April 2013 – conclusions and recommendations. (2013). Weekly Epidemiological Record, 88(20): 201–216.
6. Ministry of Health Malaysia. Yellow Fever Vaccination Centres in Malaysia. http://www.moh.gov.my/moh/images/gallery/Garispanduan/Yellow_Fever_Vaccination_Centre_in_Malaysia_new%20updated.pdf. Accessed June 2019.
7. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Updated: 10 October, 2019.
8. Roche, J.C., Jouan, A., Brisou, B., et al. (1986) Comparative clinical study of a new 17-D thermostable yellow fever vaccine. Vaccine; 4: 163-165. https://doi.org/10.1016/0264-410X(86)90004-6
9. The Malaysian National Centre of Adverse Drug Reactions Database [Accessed: 10 October, 2019]
10. World Health Organisation. (2013). Vaccines and vaccination against Yellow Fever. WHO Position Paper June 2013. Weekly Epidemiological Record, 27(88); 269-284.
11. World Health Organisation. International Health Regulations, 2005.
12. World Health Organisation (2018). International Travel And Health 15 November 2018. Vaccination requirements and recommendations for international travellers, including yellow fever and malaria. Available at https://www.who.int/ith/ithcountry-list.pdf?ua=1. Accessed March 2019.
13. World Health Organisation. Resolution WHA 67.13 and the updated Annex 7 of the IHR (2005). http://www.who.int/ith/A67_2014_Annex-7-en.pdf?ua=1. Accessed March 2019.
14. World Health Organisation. Yellow fever vaccination requirements and recommendations; malaria situation; and other vaccination requirements. Available at https://www.who.int/ith/ITH_country_list.pdf?ua=1. Accessed March 2019.
15. Zhao S, Stone L, Gao D, He D (2018) Modelling the large-scale yellow fever outbreak in Luanda, Angola, and the impact of vaccination. PLoS Negl Trop Dis 12(1): e0006158. https://doi.org/10.1371/journal.pntd.0006158

Introduction

Zoster or shingles, a dermatomal-vesicular infection, is caused by reactivation of latent varicella–zoster virus (VZV). Primary infection with VZV causes varicella. Zoster occurs following waning VZV cellular immunity and presents as a painful rash involving one or two adjacent dermatomes.

The rash is preceded by prodromal pain over the affected dermatome. It may be accompanied with headache, photophobia, malaise with fever being less common. Prodromal pain lasts three to four days but it can extend to a week. A maculopapular rash develops into clusters of vesicles. Characteristic rash appears as vesicles on an erythematous base. New vesicles continue to appear over three to four days. The rash is usually accompanied by the same pain during prodrome but this acute phase pain can worsen, improve or appear for the first time. VZV can cause viremia. In immunocompromised persons, extensive viremia can lead to disseminated form of zoster.

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster. It is diagnosed as pain persisting for an extended period after onset of zoster rash. Other complications include ophthalmic involvement, bacterial superinfections of the lesions, cranial and peripheral nerve palsies, meningoencephalitis, pneumonitis, hepatitis and acute retinal necrosis.

Vaccines

- The zoster vaccine (ZVL, **Zostavax**®) is a lyophilised preparation of Oka/Merck strain of VZV live, attenuated varicella virus (VZV). It is produced by Merck & Co. It contains hydrolysed porcine gelatine.

- **Zostavax**® vaccine is more potent than the varicella vaccine because it contains varicella virus at a much higher titre. It is not to be used for the prevention of varicella.

- The recombinant zoster vaccine (RZV, Shingrix®) is a 2-dose subunit vaccine given intramuscularly 2 to 6 months apart. It is indicated for prevention of HZ. **It is not indicated for prevention of primary varicella infection.** It consists of the major envelope glycoprotein E (gE) antigen component, which must be reconstituted at the time of use with the accompanying AS01 adjuvant suspension component to help enhance the immune response. It is produced by GSK Biologicals. This vaccine has been marketed since 2017. Although it is currently not available in Malaysia, GSK has plans to introduce the vaccine to Malaysia.

Vaccines Available in Malaysia

ZVL, Zostavax® will not be available in Malaysia soon. In future, the recombinant zoster vaccine will be available.

Contraindications and Adverse Effects

- Recombinant zoster vaccine should not be given to:
  - » Persons with a history of anaphylactic reaction to any of the vaccine components.
- To date, the reported adverse events for zoster live vaccine received by the National Pharmaceutical Regulatory Agency (NPRA) include fever and varicella like rashes.

Target Groups in Malaysia

- Recombinant zoster vaccine is recommended for persons who are 50 years and above with a history of varicella. Zoster vaccine may be given regardless of whether or not they have had prior herpes zoster (shingles) infection.

Implications for Healthcare Workers (HCWs)

Healthcare workers above 50 years should receive the vaccination as they are at higher risk of exposure to varicella-zoster virus and they may also be the source of varicella infection (chickenpox) to their patients.

Evidence for Effectiveness

- Efficacy of the recombinant zoster vaccine (RZV) was evaluated in more than 30 000 participants. The efficacy for prevention of herpes zoster was 96.9% in persons aged 50-59 years, 97.4% in persons 60-69 years and 91.3% in participants aged >70 years. In 2017, ACIP recommended it for the use of immunocompetent adults aged 50 years and above.

  In an open-label concomitant administration of recombinant zoster vaccine with influenza vaccine study, there was no evidence of interference in immune response to both vaccines.

References

1. Centers for Disease Control and Prevention. (2018) Recommendations of Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR,67,3,103-108
2. Centers for Disease Control and Prevention. (2015) Pink Book. Epidemiology and Prevention of Vaccine Preventable Disease, 13th Edition
3. Levin, M.J. (2018) Zoster vaccine. In Plotkin S.A., Orenstein W.A., Offit, P.A., Edwards K.M.(Eds) Vaccines. (7th Edition) Saunders Elsevier.
4. MSD Local Product Circular Zostervax® 2014
5. National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia. Senarai Produk Vaksin Berdaftar Dengan Pihak Berkuasa Kawalan Dadah. Updated 5 September 2019
6. The Malaysian National Centre of Adverse Drug Reactions database. Accessed: 10 October 2019

Passive Immunisation

Introduction

Passive immunisation refers to the administration of antibodies (immunoglobulins, IgG) pooled from blood donors in order to provide temporary protection in: (i) an unimmunised person exposed to an infection, and (ii) a person who has been infected from a disease for which active immunisation is not available.

The protective effect of the administered immunoglobulin is immediate but the protection may be incomplete and is short lived (lasting for several weeks up to 3–4 months).

There are 2 types of immunoglobulin that will be discussed in this guideline:

A. Normal (nonspecific) human immunoglobulin – from unselected donors.

B. Hyperimmune (specific) immunoglobulin – from selected donors.

Side effects for both immunoglobulins include malaise, chills, fever, headache, nausea, facial flushing and anaphylaxis (rare).

Normal Human Immunoglobulin (NHIg)

This is derived from the pooled plasma of blood donors. It contains antibodies against microbial agents that are prevalent in the general population. It provides antibodies against hepatitis A, rubella, measles and other viruses prevalent in the general population. It is most effective if it is administered within 72 hours or 3 days after exposure and provides immediate protection and will last several weeks. NHIg blocks the response of live vaccine (except for yellow fever) for 3 months. Therefore, live vaccines should ideally be given at least 3 weeks before or 3 months after administration of NHIg. NHIg is administered by intramuscular injection.

Today, passive immunisation with IG still plays an important part in the prevention of measles and hepatitis A among non-immune contacts in countries with low incidences of these diseases. In some cases, passive immunisation is also recommended for non-immune pregnant contacts of rubella.

There are current differences in practice with respect to passive immunisation for measles, hepatitis A and rubella contacts between the high-income countries. In Australia, immunoglobulin has not been demonstrated to be of value post-exposure. In UK and New Zealand, the use of passive immunisation in pregnant women exposed to rubella may be considered if termination of the pregnancy is not an option.

Indication for NHIg

Hepatitis A: it is given for the prevention of infection in close contacts of confirmed cases of hepatitis A, where there has been a delay of more than 7 days in identifying contacts, or for close contacts at high risk of severe disease. It is also recommended to immunocompromised patients whose antibody response to vaccine is unlikely to be adequate. It is preferably given within the first 72 hours of exposure.

Measles: NHIg may be given to prevent or attenuate a measles attack in individuals who do not have adequate immunity (immunocompromised adults and children) who were in close contact with patients infected with measles. It is most effective if given within 72 hours of exposure but can still be given up to 6 days of post exposure.

NHIg should also be considered in the following patients if they have been in contact with a confirmed case of measles or with a person associated with a local outbreak: (i) non-immune pregnant women, and (ii) Infants under 9 months old.

Individuals with normal immunity who are not in the above categories and who have not been fully immunised against measles, can be given measles vaccination.

Rubella: NHIg given after exposure to rubella does not prevent infection in non-immune contact and it is not recommended for protection of pregnant women exposed to rubella. It may, however, reduce the likelihood of clinical attack in pregnant woman which may possibly reduce the risk to the foetus. It should be used ONLY in pregnant women when termination is unacceptable. Serological follow up of recipients is important to determine if the woman has become infected despite receiving NHIg.

- For healthy persons aged 12 months–40 years, single-antigen Hepatitis A vaccine at the age-appropriate dose is preferred to IG because of the vaccine's advantages, including long-term protection and ease of administration, as well as the equivalent efficacy of vaccine to IG.
- For persons aged 41 years and older, IG is preferred because of the absence of information regarding vaccine performance in this age group and because of the more severe manifestations of Hepatitis A in older adults. The magnitude of the risk of HAV transmission from the exposure should be considered in decisions to use vaccine or IG in this age group.
- Vaccine can be used if IG cannot be obtained.
- IG should be used for children aged less than 12 months, immunocompromised persons, persons with chronic liver disease, and persons who are allergic to the vaccine or a vaccine component.

Summary Table 19.1
Normal Human Immunoglobulin (NHIg)

Infection	Indication	Target population	IG dosage
Hepatitis A	Contacts for post exposure passive immunisation	Within 2 weeks of last exposure to an infectious case: • 41 years or older of age • vaccine is contraindicated	0.02 ml/kg
Measles	Contacts for post exposure passive immunisation	Up to 6 d after first exposure if: • >72 h since first contact with case • pregnant • immunosuppressed • vaccine contraindicated	0.25 ml/kg (max = 15 ml) Immunocompromised: 0.5 ml/kg (max = 15 ml)
Rubella	Contacts for post exposure passive immunisation	• Consider only if pregnant woman exposed to rubella and will not consider termination under any circumstances. In these cases, administer immunoglobulin within 72 h of exposure	20 mL in divided doses

Summary Table 19.2
Specific Immunoglobulins

Products	Indication	Comments
Diphtheria antitoxin	Is administered before bacteriologic confirmation when there is a clinical suspicion of the disease.	It is not recommended for prophylactic use in close, unimmunised contacts of diphtheria cases.
Hepatitis B Ig (HBIg)	HBIg is recommended for the following: • Acute percutaneous or mucosal exposure to blood containing HBV (HbS Ag+) – needle stick, bite. • People who have had unprotected sex with a person with acute or chronic HBV infection. • Infants <12 mo whose family members are $HBsAg^{+}$. • Newborns to mothers with acute or chronic HBV infection or whose mothers are at high risk of infection with hepatitis B.	HBIg provides immediate, short-term protection against hepatitis B infection. It can prevent illness or make the illness less severe. A dose of hepatitis B vaccine may be given at the same time as HBIg. Two more doses of hepatitis B vaccine may be given later to provide full, long-term protection against infection. When administered to the baby of a mother with acute or chronic HBV infection, HBIg has to be administered within 12 hours of birth and given with the 1st dose of hepatitis B vaccine. HBIg works best if given as soon as possible and within 14 days after exposure to the hepatitis B virus.

Products	Indication	Comments
Varicella zoster Ig (VZIg)	Persons who are at greater risk for severe complications, not candidates for varicella vaccination, may or may not benefit from post-exposure prophylaxis VZIg include: • Susceptible immunocompromised persons. • Patients treated with long-term corticosteroids >2mg/kg of body weight or total of 20mg/day of prednisolone or equivalent. • Susceptible pregnant women.	• The decision to administer VZIg to a person exposed to varicella should be based on whether: (i) the patient is susceptible, (ii) the exposure is likely to result in infection, (iii) the person is at greater risk for complications than in general population. • VZIg should be administered as soon as possible after exposure but may also be effective if given up to 96 hours after exposure
Rabies Ig	Post exposure prophylaxis of rabies.	For individuals suspected of exposure to rabies, particularly severe exposure, with one exception i.e. persons who have been previously immunised with rabies vaccine.
Human Tetanus Ig	Tetanus prone wounds and all wounds if the individual is thought to be non-immune. All wounds, other than clean minor wounds, should be considered tetanus-prone. Newborns whose umbilical cords are cut by unsterilised instruments.	Tetanus is a medical emergency and requires immediate treatment with human tetanus Ig, an anti-tetanus toxoid booster, agents to control the muscle spasm, aggressive wound care and antibiotics. It is given as part of the management of wounds if there is heavy soil contamination and all wounds if the individual is thought to be non-immune.

Note: Ig – Immune globulin, HBV - Hepatitis B virus

Table 19.3
Notes on Passive Immunisation for Immunocompromised Hosts (ICH)

Subgroup at risk	Ig	Recommendation	Additional comments
Primary hypogamma-globulinaemia	IV NHIg	• 0.4-0.6 g/kg, every 4 weeks	• In general, replacement therapy is initiated if serum Ig level < 150 mg/dl (severe hypogammaglo-bulinaemia)
Secondary hypogammaglo-bulinaemia with recurrent severe infections (>2 episodes/year)	IV NHIg		• This include patients with multiple myeloma, recipients of hematopoietic stem cell transplantation
ICH exposed to Measles	IV NHIg	• IM 0.25-0.5mL/kg (max 15mL) administered as soon as possible (within 6 days after exposure) regardless of previous vaccination status	• IM NHIg may not be necessary for patients who are receiving IV NHIg at regular intervals and the last dose was administered within 3 weeks of exposure
ICH Hepatitis A	IV NHIg	• IM 0.02mL/kg (max 15mL) administered as soon as possible (within 2 weeks of exposure)	

ICH exposed to Hepatitis B	HBIg	• IM 0.06mL/kg as soon as possible after exposure preferably within 48 hours of exposure but up to 2 weeks from last known sexual contact • If Hepatitis B vaccine series has not been started, a 2nd dose of HBIg should be administered one month later (for percutaneous/ mucous membrane exposure) or 3 months after sexual exposure	
ICH exposed to Varicella zoster	VZIg	• IM 125units/10kg (max 625 units) administered as soon as possible or within 96 hours of contact	• Definition of contact: Household contact; Close contact indoors >1 hour sharing 2-4 bed hospital cubicle/room; Prolonged direct face-to-face contact (eg doctor/ nurse and patient)

Subgroup at risk	Ig	Recommendation	Additional comments
ICH with unknown/ inadequate tetanus vaccination status and a non-clean, non- minor wound	TIg	• For wound <24 hours: IM250 units; • For wound >24 hours or heavy contamination – IM500 units	• Inadequate tetanus vaccination is defined as less than 2 doses of tetanus vaccine previously
ICH exposed to rabies and with unknown vaccination status	RIg	• 20IU/kg, (human RIG or 40 IU/kg Horse RIG) up to half to be infiltrated around the wound	• IM rabies vaccine to be given on days 0, 3, 7, 14 – 28

References

1. Baxter, D. (2007). Active and passive immunity, vaccine types, excipients and licensing. Occupational Medicine, 57(8), 552-556.
2. Buckley, R. H., & Schiff, R. I. (1991). The use of intravenous immune globulin in immunodeficiency diseases. New England Journal of Medicine, 325(2), 110-117.
3. Organization, W. H. (2018). Rabies vaccines: WHO position paper, April 2018–Recommendations. Vaccine, 36(37), 5500-5503.
4. Perez, E. E., Orange, J. S., Bonilla, F., Chinen, J., Chinn, I. K., Dorsey, M., El-Gamal, Y., Harville, T. O., Hossny, E., & Mazer, B. (2017). Update on the use of immunoglobulin in human disease: a review of evidence. Journal of Allergy and Clinical Immunology, 139(3), S1-S46.
5. Practices, A. C. o. I. (2007). Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee.
6. Young, M. K., & Cripps, A. W. (2013). Passive immunization for the public health control of communicable diseases: current status in four high-income countries and where to next. Human vaccines & immunotherapeutics, 9(9), 1885-1893.

Upcoming Vaccines

Avian Influenza

Introduction

Avian influenza causes two forms of disease in poultry, one common and mild, the other rare but highly lethal. While 16 HA and 9 NA virus subtypes infect birds, the highly pathogenic viruses (HPAI) are typically H5 and H7 subtypes. Avian influenza viruses are normally species specific, but five strains (H5N1, H7N3, H7N7, H7N9 and H9N2) have infected humans. H5N1 virus can cause severe disease and death in humans, and has appeared in more than 60 countries across Asia, Europe and Africa. H5N1 spreads rapidly in bird populations worldwide and there is great concern that this virus will begin to transmit between humans and cause a global pandemic. However, no information is available on the likelihood of occurrence of an H5N1 pandemic and the severity of such a pandemic.

Based on limited epidemiological data, the overall risk of HPAI H5N1 virus transmission to humans following exposure to the virus appears to be very low. The key factors are the intensity of exposure to the virus, potentially modifiable factors such as behaviour or use of protective equipment, and possibly other unknown host factors.

Vaccines are the cornerstone strategy for combating avian influenza. However, there are challenges for pandemic preparedness including the unpredictability of the vaccine target, the potential production capacity for pandemic vaccine, manufacturing requirement for rapid deployment, as well as expiry of stockpiled vaccines during interpandemic period.

Vaccines

The initial H5N1 vaccines were produced using the same manufacturing methods and regulatory approval criteria as seasonal influenza vaccines, which involves production of a virus seed stock optimised for growth in chicken eggs and inactivation. The inactivated H5N1 vaccines are poorly immunogenic and are inefficiently produced. New vaccine technologies are under research, which will maximise antigen activity and expedite vaccine supply. New egg-independent vaccine antigens that appear effective in human clinical trials include cell-based virus production, recombinant protein and virus-like particles. Vaccine adjuvants augment adaptive immunity and are being used to broaden antibody responses against different strains of virus and to improve vaccine dose-sparing.

Several H5N1 influenza vaccines have been registered for use in interpandemic period, such as the following:

i. GlaxoSmithKline's vaccine Prepandrix® approved by the European Union in May 2008.

ii. CSL Limited's vaccine Panvax® approved by Australia in June 2008.

iii. Sanofi Pasteur's vaccine approved by the United States in April 2017.

The use of the vaccines during in interpandemic period should be based on risk assessment:

- Vaccination with licensed H5N1 vaccine is strongly recommended for laboratory workers involved in the following activities:
  - » large-scale production or manipulation of HPAI H5N1 virus;
  - » working with the virus over a long period;
  - » working with HPAI H5N1 virus strains that are resistant to licensed antiviral compounds;
  - » working with virus strains with the potential for increased transmissibility in mammalian species.

For laboratory personnel working with H5N1 virus, but not involved in these activities, the risks and benefits associated with H5N1 vaccination should be evaluated.

- Vaccine may be made available to HCWs in countries where avian H5N1 virus is enzootic and where human cases may continue to emerge and pose the threat of exposure for HCWs.
- Vaccination is recommended for HCWs who evaluate or manage suspected or confirmed H5N1 patients in designated outpatient or inpatient referral facilities.
- Vaccination is recommended for workers involved in a first response to possible H5N1 outbreaks in animals or humans, depending on the assumed risk of exposure and type of activities.
- Vaccine may be made available as a preventive measure to the relatively few persons in contact with poultry in confirmed active outbreak areas, depending on the level of enzooticity, risk of exposure and effectiveness of other prevention measures in place.
- The risk of infection in the general public remains very low. Since one cannot exclude a risk, albeit low, of vaccine-related serious adverse events, and at the present low level of risk of infection, H5N1 vaccination is not recommended currently in the general population.

Vaccines are critical for preventing influenza disease, but significant scientific and economic challenges remain in providing universal coverage of a pandemic influenza vaccine on a global scale. Vaccine development is challenged by the unpredictability of the emerging strain of virus, the fact that humans will likely not be immune to the virus, and that manufacturing capacity will be insufficient to meet worldwide demand. Better, faster and more efficient ways are under study in vaccines development. There is a need for new recombinant-based vaccines and adjuvants that can maximise immunogenicity, shorten production cycles and satisfy global demand. All available technologies will be needed in order to produce a world supply of vaccine within 6 months of a pandemic outbreak. A careful risk assessment is required for H5N1 vaccination during interpandemic period.

References

1. Clegg, C. H., Rininger, J. A., & Baldwin, S. L. (2013). Clinical vaccine development for H5N1 influenza. Expert review of vaccines, 12(7), 767–777. https://doi.org/10.1586/14760584.2013.811178
2. Steel J. (2011). New strategies for the development of H5N1 subtype influenza vaccines: progress and challenges. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*, 25(5), 285–298. https://doi.org/10.1007/BF03256169
3. Strategic Advisory Group of Experts. (2009). Report of the H5N1 SAGE Working Group to the April 2009 meeting. Use of licensed H5N1 influenza vaccines in the interpandemic period. Available at https://www.who.int/immunization/sage/SAGE_ H5N1_26Mayb.pdf. Accessed April 2019.

Chikungunya

Introduction

Chikungunya is a mosquito-borne viral disease caused by the chikungunya virus (CHIKV), a *Togaviridae* virus. During epidemics and endemic circulation, CHIKV is transmitted by *Aedes aegypti* and, to a lesser extent, by *A. albopictus* mosquitoes. In Asia, CHIKV is endemic and causes recurrent and sometimes large epidemics, especially in the Indian subcontinent and in Southeast Asia. The number of reported Chikungunya cases in Malaysia is shown in Table 20.3.1

Table 20.3.1
The number of reported Chikungunya cases in Malaysia (MOH 2020)

Year	No of cases
2008	4,271
2009	5,430
2010	804
2011	30
2012	93
2013	7
2014	7
2015	3
2016	12
2017	270
2018	87
2019	990
2020 (as of 10 October)	2277

Chikungunya virus causes clinical illness in 72% to 92% of infected humans around four to seven days after an infected mosquito bite. Infection with CHIKV typically causes a self-limiting febrile illness, acute onset of fever, characterised by chronic, severe joint and muscle pain, and sometimes accompanied by an itchy maculopapular skin rash. Severe complications, such as encephalitis, may occur in the elderly and in individuals with comorbidities. Peripartum infections can be fatal or involve severe neurologic sequelae in foetuses and infants. Persistent arthralgia and joint swelling are common long-term manifestations of CHIKV infection. Fatalities have been reported (case fatality rates of 0.1% to 4.9% from epidemics) in elderly patients, who are at a higher risk.

There is no specific treatment available, and no licensed vaccines to specifically target CHIKV disease. Prevention of transmission is based on vector control, which is challenging especially in developing countries. Due to the epidemic potential, the impact of CHIKV infection in terms of burden of disease, work and school absenteeism, and other financial costs is particularly high.

Vaccines

There is no commercial vaccine against CHIKV at present. Several inactivated and attenuated vaccine candidates and a variety of strategies have been tested in preclinical and human trials, with promising results. The CHIKV antigen variety is limited and infection may lead to lifelong immunity. The potential vaccine candidates are classified into seven types: inactivated vaccine, subunit vaccine, live attenuated vaccine, recombinant virus-vectored vaccine, virus-like particle vaccine, chimeric vaccine, and nucleic acid vaccine. About 30 vaccine candidates have been reported, but only a few have entered Phase 1 or 2 trials.

i. **TSI-GSD-218 (181/clone25)**
Developed by United States Army Medical Research Institute of Infectious Diseases. It is a live-attenuated CHIKV strain, which completed Phase 2 trial.

ii. **VRC-CHKVLP059-00-VP (PXVX0317 CHIKV-VLP)**
Developed by US National Institutes of Health. Virus-like particles (VLPs), assembled from CHIKV proteins expressed in mammalian cells. Currently in Phase 2 trial.

iii. **MV-CHIK**
Developed by Institut Pasteur, Themis Bioscience. Viral vector vaccine, which is a recombinant live-attenuated measles vaccine as a vector, expressing CHIKV virus-like particles derived from the structural protein genes. Currently in Phase 2 trial.

Although VLP- and MV-based vaccines have high safety profiles, the cost of production and the potential requirement for additional boosters may hinder widespread use in low-resource countries where CHIKV is endemic.

References

1. Chang, L. J., Dowd, K. A., Mendoza, F. H., Saunders, J. G., Sitar, S., Plummer, S. H., Yamshchikov, G., Sarwar, U. N., Hu, Z., Enama, M. E., Bailer, R. T., Koup, R. A., Schwartz, R. M., Akahata, W., Nabel, G. J., Mascola, J. R., Pierson, T. C., Graham, B. S., Ledgerwood, J. E., & VRC 311 Study Team (2014). Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. Lancet (London, England), 384(9959), 2046–2052. https://doi.org/10.1016/S0140-6736(14)61185-5
2. Erasmus, J. H., Rossi, S. L., & Weaver, S. C. (2016). Development of Vaccines for Chikungunya Fever. The Journal of infectious diseases, 214(suppl 5), S488–S496. https://doi.org/10.1093/infdis/jiw271
3. Gao, S., Song, S., & Zhang, L. (2019). Recent Progress in Vaccine Development Against Chikungunya Virus. Frontiers in microbiology, 10, 2881. https://doi.org/10.3389/fmicb.2019.02881
4. Powers A. M. (2017). Vaccine and Therapeutic Options To Control Chikungunya Virus. Clinical microbiology reviews, 31(1), e00104-16. https://doi.org/10.1128/CMR.00104-16
5. Ramsauer, K., Schwameis, M., Firbas, C., Müllner, M., Putnak, R. J., Thomas, S. J., Desprès, P., Tauber, E., Jilma, B., & Tangy, F. (2015). Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial. The Lancet. Infectious diseases, 15(5), 519–527. https://doi.org/10.1016/S1473-3099(15)70043-5
6. Rezza, G., & Weaver, S. C. (2019). Chikungunya as a paradigm for emerging viral diseases: Evaluating disease impact and hurdles to vaccine development. PLoS neglected tropical diseases, 13(1), e0006919. https://doi.org/10.1371/journal.pntd.0006919
7. Smalley, C., Erasmus, J. H., Chesson, C. B., & Beasley, D. (2016). Status of research and development of vaccines for chikungunya. Vaccine, 34(26), 2976–2981. https://doi.org/10.1016/j.vaccine.2016.03.076
8. Weaver, S. C., & Lecuit, M. (2015). Chikungunya virus and the global spread of a mosquito-borne disease. The New England journal of medicine, 372(13), 1231–1239. https://doi.org/10.1056/NEJMra1406035
9. Yang, S., Fink, D., Hulse, A., & Pratt, R. D. (2017). Regulatory considerations in development of vaccines to prevent disease caused by Chikungunya virus. Vaccine, 35(37), 4851–4858. https://doi.org/10.1016/j.vaccine.2017.07.065

Clostridioides difficile

Introduction

Clostridioides difficile (formerly *Clostridium difficile*) infection (CDI) is a major cause of antibiotic-associated diarrhoea and colitis and the most common pathogen in healthcare-associated infections. The spectrum of CDI ranges from asymptomatic carriage and mild diarrhoea to life-threatening pseudomembranous colitis, toxic megacolon, and fulminant colitis. Long-term resolution of symptoms is difficult to achieve in a large percentage of patients with CDI, where approximately 20% of patients with CDI experience recurrent infections after responding to initial therapy. The infection is associated with antibiotic use in healthcare settings, but has increasingly occurred in the community since the emergence of hypervirulent strains since the early 2000's.

Antibodies to TcdA and TcdB confer protection against primary CDI and recurrences. Bezlotoxumab is a monoclonal antibody against TcdB recently approved by the US FDA, which reduces the rate of CDI recurrence in adults.

Vaccines

Currently no vaccine is registered. There are 3 candidate vaccines undergoing phase 2 and 3 clinical evaluation for CDI prevention.

1. The Sanofi Pasteur toxoid vaccine uses formalin-inactivated full-length TcdA and TcdB administered by intramuscular injection at days 0, 7 and 30. In phase 2 trials, the vaccine was safely administered to adults older than 50, and seroconversion to TcdA and TcdB was 97% and 92% respectively. The high-dose adjuvanted vaccine has demonstrated elevated circulating titers for up to 3 years after the last dose of the primary series given at 0, 7, and 30 days.

The Phase 3 programme known as Cdiffense was discontinued by Sanofi Pasteur in December 2017. The multicentre, observer-blind, randomised, controlled trial was conducted at 326 hospitals, clinics, and clinical research centres in 27 countries in the USA, Canada, Latin America, Europe, and the Asia-Pacific region. It evaluated single injections of high-dose plus adjuvant vaccine, in about 16,500 adult volunteers at least 50 years old, who are at risk of CDI. Secondary endpoints include the number of PCR-confirmed primary CDI cases after two and three injections, maximum number of loose stools per day, CDI episode/illness duration, immunogenicity and injection site and systemic reactions. Prior Phase 2 trials demonstrated high rates of seroconversion (over 90%), but did not translate into protection against the disease during the Phase 3 trial. In adults at risk for *C. difficile* infection, the bivalent *C. difficile* toxoid vaccine did not prevent *C. difficile* infection. Since the vaccine candidate met the criteria for futility, the study was terminated and clinical development of this vaccine candidate was stopped.

2. The vaccine being developed by Pfizer targets toxins A and B of *C. difficile*. *Clostridium difficile* Vaccine Efficacy Trial (CLOVER), a phase 3 clinical efficacy and safety study was started in early 2017 in over 20 countries globally. Completion is expected at the end of 2020. Subjects enrolled were 50 years of age and older who are at higher risk for CDI, consisting of about 16,000 participants.

   The phase 2 trial which studied the safety, tolerability, and immunogenicity in 855 older US adults of the bivalent *C. difficile* vaccine was conducted from July 2015 through March 2017, in 15 US centres. It was shown that the *C. difficile* vaccine was safe, well tolerated, and immunogenic in healthy adults aged 65-85 years. These results support continued vaccine development. However, having similar toxoid-based mechanism of action to Sanofi's vaccine, it raises doubt whether the seroconversion observed in Phase II trials can translate into clinical efficacy. Pfizer plans to investigate rates of both primary and recurrent infections.

3. Valneva has developed toxins A and B into a single recombinant subunit protein or a fusion protein, containing the toxin A and B receptor binding domains. Valneva successfully completed Phase 2 development of its vaccine candidate VLA84.

   The Phase 2 trial was a randomized, placebo-controlled, observer-blind multi-center trial with 500 subjects, designed to further study and confirm the candidate vaccine's safety, immunogenicity and proposed doses of immunisations in two different age groups (50 to 64 years of age and 65 years of age and older). Final Phase 2 results of this vaccine candidate confirm positive initial Phase 2 data that were released at the end of 2015. VLA84 was immunogenic at all doses and formulations tested, in that Immunoglobulin G (IgG) and functional (neutralising) antibody responses were observed. The study met its primary endpoint in terms of identifying the dose/formulation with the highest seroconversion rate against both toxins A and B and confirmed the favourable safety profile observed in Phase 1. VLA84 is currently Phase 3-ready.

Table 20.2.1
***C. difficile* vaccines in clinical development**

Vaccine product	Antigen	Formulation and schedule	Target Population	Clinical trial
Sanofi Pasteur, C. *difficile* toxoid vaccine	Formalin-inactivated toxins A and B from VPI 10463	Intramuscular injection days 0, 7 and 30	Age >50 years	Phase 3 Cdiffense trial discontinued in December 2017
Pfizer, C. *difficile* vaccine PF-06425090	Genetically modified and chemically treated recombinant vaccine	+/- Adjuvant, intramuscular injection days 1, 8 and 30	Age 50–85 years	Phase 3

Vaccine product	Antigen	Formulation and schedule	Target Population	Clinical trial
Valneva, VLA84 *C. difficile* vaccine	Recombinant fusion protein of toxin A and B binding regions	+/- Aluminium adjuvant, intramuscular injection days 0, 7 and 28	Age 50–64 years Age >65 years	Phase 2 completed in 2016

Adapted from:

Kociolek LK, Gerding DN. Breakthroughs in the treatment and prevention of *Clostridium difficile* infections. Nat Rev Gastroenterol Hepatol. 2016; 13:150-160.

Further research is needed on *C. difficile* vaccine efficacy. Vaccine candidates targeting toxins A and B might prevent clinical illness but may not alter gastrointestinal tract colonisation. Prevention of *C. difficile* colonisation has generated interest in targeting non-toxin surface protein antigens. Other areas include the cross-reactivity of antibodies to antigens among different *C. difficile* strains, the need for adjuvants and the specific types of adjuvants, the optimal age for immunisation, demonstration of immune response in high-risk elderly individuals, and the duration of protection in humans.

References

1. Bézay, N., Ayad, A., Dubischar, K., Firbas, C., Hochreiter, R., Kiermayr, S., Kiss, I., Pinl, F., Jilma, B., & Westritschnig, K. (2016). Safety, immunogenicity and dose response of VLA84, a new vaccine candidate against Clostridium difficile, in healthy volunteers. Vaccine, 34(23), 2585–2592. https://doi.org/10.1016/j.vaccine.2016.03.098
2. de Bruyn, G., Gordon, D. L., Steiner, T., Tambyah, P., Cosgrove, C., Martens, M., Bassily, E., Chan, E.S., Patel, D., Chen, J., Torre-Cisneros, J., Francesconi, C.F., .. Gurunathan, S. (2020). Safety, immunogenicity, and efficacy of a clostridioides difficile toxoid vaccine candidate: A phase 3 multicentre, observer-blind, randomised, controlled trial. The Lancet Infectious Diseases, doi:10.1016/S1473-3099(20)30331-5
3. de Bruyn, G., Saleh, J., Workman, D., Pollak, R., Elinoff, V., Fraser, N. J., Lefebvre, G., Martens, M., Mills, R. E., Nathan, R., Trevino, M., van Cleeff, M., Foglia, G., Ozol-Godfrey, A., Patel, D. M., Pietrobon, P. J., Gesser, R., & H-030-012 Clinical Investigator Study Team (2016). Defining the optimal formulation and schedule of a candidate toxoid vaccine against Clostridium difficile infection: A randomized Phase 2 clinical trial. Vaccine, 34(19), 2170–2178. https://doi.org/10.1016/j.vaccine.2016.03.028
4. Ghose, C., & Kelly, C. P. (2015). The prospect for vaccines to prevent Clostridium difficile infection. Infectious disease clinics of North America, 29(1), 145–162. https://doi.org/10.1016/j.idc.2014.11.013
5. Henderson, M., Bragg, A., Fahim, G., Shah, M., & Hermes-DeSantis, E. R. (2017). A Review of the Safety and Efficacy of Vaccines as Prophylaxis for Clostridium difficile Infections. Vaccines, 5(3), 25. https://doi.org/10.3390/vaccines5030025
6. Kitchin, N., Remich, S. A., Peterson, J., Peng, Y., Gruber, W. C., Jansen, K. U., Pride, M. W., Anderson, A. S., Knirsch, C., & Webber, C. (2020). A Phase 2 Study Evaluating the Safety, Tolerability, and Immunogenicity of Two 3-Dose Regimens of a Clostridium difficile Vaccine in Healthy US Adults Aged 65 to 85 Years. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 70(1), 1–10. https://doi.org/10.1093/cid/ciz153
7. Kociolek, L. K., & Gerding, D. N. (2016). Breakthroughs in the treatment and prevention of Clostridium difficile infection. Nature reviews. Gastroenterology & hepatology, 13(3), 150–160. https://doi.org/10.1038/nrgastro.2015.220
8. Sheldon, E., Kitchin, N., Peng, Y., Eiden, J., Gruber, W., Johnson, E., Jansen, K. U., Pride, M. W., & Pedneault, L. (2016). A phase 1, placebo-controlled, randomized study of the safety, tolerability, and immunogenicity of a Clostridium difficile vaccine administered with or without aluminum hydroxide in healthy adults. Vaccine, 34(18), 2082–2091. https://doi.org/10.1016/j.vaccine.2016.03.010
9. Wilcox, M. H., Gerding, D. N., Poxton, I. R., Kelly, C., Nathan, R., Birch, T., Cornely, O. A., Rahav, G., Bouza, E., Lee, C., Jenkin, G., Jensen, W., Kim, Y. S., Yoshida, J., Gabryelski, L., Pedley, A., Eves, K., Tipping, R., Guris, D., Kartsonis, N., ... MODIFY I and MODIFY II Investigators (2017). Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection. The New England journal of medicine, 376(4), 305–317. https://doi.org/10.1056/NEJMoa1602615

COVID-19

Introduction

The current pandemic of COVID-19, caused by SARS-CoV-2 virus is a global epidemiological crisis. The viral infection has affected about 215 countries and territories around the world. In just over 7 months after the pandemic was declared in March 2020, there are more than 47.3 million cases worldwide and more than 1.21 million deaths. There is also the possibility of the disease becoming endemic and seasonal, according to some experts. Many research groups and companies globally are undertaking efforts to develop a safe and effective vaccine, at an unprecedented speed for the usual phases needed to develop and test a vaccine in humans.

Vaccines

No vaccine is currently available for prevention of any coronavirus infection in humans. Previous attempts to develop vaccines for Coronaviridae virus family that infect humans have been for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The vaccines candidates have been tested in animals. As of 2020, there is still no vaccine proven to be safe and effective against SARS or MERS.

Most of the platforms of vaccine candidates for COVID-19 in clinical trials as of September 2020 are focused on the coronavirus spike protein and its variants as the primary antigen. Vaccine strategies being rapidly developed involve nucleic acid technologies (RNA and DNA), peptides, recombinant proteins, non-replicating viral vectors, live attenuated viruses, and inactivated viruses. A safe and effective coronavirus vaccine is targeted by 2021. Research teams are currently testing more than 40 vaccines in clinical trials on humans, and more than 90 vaccines are investigated in preclinical phases in animals.

Upcoming Vaccines

Several organizations have joined forces in the face of the pandemic with the aim to reduce mortality and severe disease. COVAX is a global initiative co-led by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, the Vaccine Alliance, and the World Health Organization (WHO). COVAX works in partnership with governments and manufacturers to ensure COVID-19 vaccines are available worldwide to both higher-income and lower-income countries, once they are licensed and approved. The coalition aims to provide two billion doses of vaccine to the most vulnerable people and to health-care workers, especially in poor countries. More than 170 economies are now engaged in discussions to potentially participate in COVAX, including Malaysia. Currently, CEPI's candidates include the companies Inovio, Moderna, CureVac, Institut Pasteur/Merck/Themis, AstraZeneca/University of Oxford, Novavax, University of Hong Kong, Clover Biopharmaceuticals, and University of Queensland/CSL which are part of the COVAX initiative. The Access to COVID-19 Tools (ACT) Accelerator, is a ground-breaking global collaboration to accelerate development, production, and equitable access to COVID-19 tests, treatments, vaccines and health system strengthening.

In early October 2020, China announced that it had joined COVAX. About 80 other wealthy countries have committed to support the initiative. The Malaysian government is also planning to join the COVAX vaccine access plan. COVAX facility would provide vaccine doses for only ten per cent of the total population, or three million residents in Malaysia. The plan operates on a two-dose regimen, which means that vaccinating 10 per cent of Malaysia's population amounts to six million doses.

Two vaccines co-developed by China pharmaceutical group Sinopharm and other groups is targeted to be available at the end of 2020. The vaccines are being tested in several countries including the United Arab Emirates, Bahrain, Peru and Argentina. Sinopharm said it may have the capacity to produce more than 1 billion doses in 2021. In addition, hundreds of thousands of people in China have been given experimental trial-stage vaccines as part of an emergency inoculation programme launched in July 2020.

There are currently more than 100 COVID-19 vaccine candidates under development, some of which are in the human trial or clinical phase. Combining phases of the clinical trial is a way to accelerate vaccine development. For instance, some coronavirus vaccines are now in Phase 1/2 trials, in which they are tested for the first time on hundreds of people (testing safety and dosage, plus expanded safety trials). Some candidate vaccines have reached phase 3, which is large scale assessment of efficacy and safety. Development and progress in this area is rapidly changing.

Vaccine candidates that have entered Phase 3:

1. **CanSino Biologics,** a Chinese company developed a viral vector vaccine based on Ad5 adenovirus, in collaboration with the Institute of Biology at the **Academy of Military Medical Sciences**.
2. **Gamaleya Research Institute**, part of Russia's Ministry of Health, launched clinical trials in June for Gam-Covid-Vac (Sputnik V). The vaccine is based on two adenovirus viral vectors, Ad5 and Ad26, with coronavirus protein.
3. **Wuhan Institute of Biological Products** developed an inactivated virus vaccine, which the state-owned Chinese company **Sinopharm** tested in clinical trials.
4. **Beijing Institute of Biological Products** developed an inactivated virus vaccine, also tested by **Sinopharm** in clinical trials.
5. **Sinovac Biotech**, a private Chinese company is testing an inactivated vaccine called CoronaVac.
6. **Moderna** in collaboration with the **National Institutes of Health**, develops vaccines based on messenger RNA (mRNA) to produce viral proteins in the body.
7. **BioNTech**, a German company partnered with **Pfizer**, based in New York, and the Chinese drug company **Fosun Pharma** to develop an mRNA vaccine.
8. **Johnson & Johnson** developed adenovector Ad26 candidate vaccine, which builds on the technology used for Ebola, Zika and HIV vaccines.
9. **AstraZeneca**, the British-Swedish company with the **University of Oxford** developed a viral vector vaccine ("Trojan horse") based on a chimpanzee adenovirus, called ChAdOx1.

10. **Novavax** based in Maryland, USA makes vaccines by bioengineering the spike protein and combination into nanoparticles.
11. **Murdoch Children's Research Institute** in Australia is conducting a Phase 3 trial called BRACE, to study the Bacillus Calmette-Guerin vaccine and its protection against the coronavirus. The vaccine is live-attenuated and was developed in the early 1900s as a protection against tuberculosis.
12. **Bharat Biotech** and the **National Institute of Virology** in India developed an inactivated vaccine called Covaxin.

To date, the above vaccines Nos. **1-5** have been granted early or limited approval. Russia became the first country to give regulatory approval to a Covid-19 vaccine (Sputnik V) in August 2020. In addition, Russia has given regulatory approval to another vaccine called EpiVacCorona, prior to reaching Phase 3. This vaccine contains chemically synthesized viral peptide antigens (Phase 1/2). The vaccine was developed by **The Vector Institute**, a Russian biological research center.

References

1. Bar-Zeev, N., & Inglesby, T. (2020). COVID-19 vaccines: early success and remaining challenges. The Lancet, 396(10255), 868-869. https://doi.org/10.1016/S0140-6736(20)31867-5
2. Calina, D., Docea, A.O., Petrakis, D., Egorov, A.M., Ishmukhametov, A.A., Gabibov, A.G..Tsatsakis, A. (2020). Towards effective COVID 19 vaccines: Updates, perspectives and challenges (Review). International Journal of Molecular Medicine, 46, 3-16. https://doi.org/10.3892/ijmm.2020.4596
3. Craven J. (2020). COVID-19 vaccine tracker. Available at https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker. Accessed 30 October 2020.
4. Lurie, N., Saville, M., Hatchett, R., & Halton, J. (2020). Developing Covid-19 Vaccines at Pandemic Speed. The New England journal of medicine, 382(21), 1969–1973. https://doi.org/10.1056/NEJMp2005630
5. Mello, M. M., Silverman, R. D., & Omer, S. B. (2020). Ensuring Uptake of Vaccines against SARS-CoV-2. The New England journal of medicine, 383(14), 1296–1299. https://doi.org/10.1056/NEJMp2020926
6. Peiris, M., & Leung, G. M. (2020). What can we expect from first-generation COVID-19 vaccines?. Lancet (London, England), S0140-6736(20)31976-0. Advance online publication. https://doi.org/10.1016/S0140-6736(20)31976-0
7. The New York Times (2020). Coronavirus Vaccine Tracker. Available at https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html
8. World Health Organisation (2020). COVAX: Working for global equitable access to COVID-19 vaccines. Available at https://www.who.int/initiatives/act-accelerator/covax. Accessed October 2020.
9. World Health Organisation (2020). The push for a COVID-19 vaccine. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines. Accessed October 2020.
10. Wu S. C. (2020). Progress and Concept for COVID-19 Vaccine Development. Biotechnology journal, 15(6), e2000147. https://doi.org/10.1002/biot.202000147

Dengue

Introduction

Dengue virus (DENV), a member of the genus Flavivirus, is the causative agent of dengue fever and the more severe and potentially life-threatening dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). DENV is endemic in South and Central America, Southeast Asia and Sub-Saharan Africa, and is one of the World Health Organization's top ten threats to global health in 2019. Approximately half of the world is at risk of dengue, which is estimated to cause 390 million infections and 20,000 deaths globally each year.

In Malaysia, the cumulative number of 130,101 dengue cases with 182 deaths has been reported in 2019. In 2018 a total of 80,615 cases of dengue fever was recorded, with 147 deaths. Dengue cases and deaths in Malaysia (2000 – 2019) is shown in Figure 20.4.1 on page 202. Dengue cases reported weekly in 2019 and 2020 is shown in Figure 20.4.2 on page 203.

Dengue is spread by *Aedes aegypti* and *Aedes albopictus* mosquitoes. There are 4 genetically and immunologically distinct serotypes: dengue-1 virus (DENV1), dengue-2 virus (DENV2), dengue-3 virus (DENV3) and dengue-4 virus (DENV4). The prevalence of individual serotypes varies across different regions, countries, seasons and over time. Recovery from infection by one serotype provides lifelong immunity against only that serotype, and subsequent infections by heterologous serotypes give rise to the potential immunopathology of severe dengue due to antibody-dependent enhancement. Patients with a second dengue infection with a different serotype are at increased risk for severe dengue. One of the challenges to the development of a dengue vaccine is that it must induce immunity to all 4 serotypes.

Upcoming Vaccines

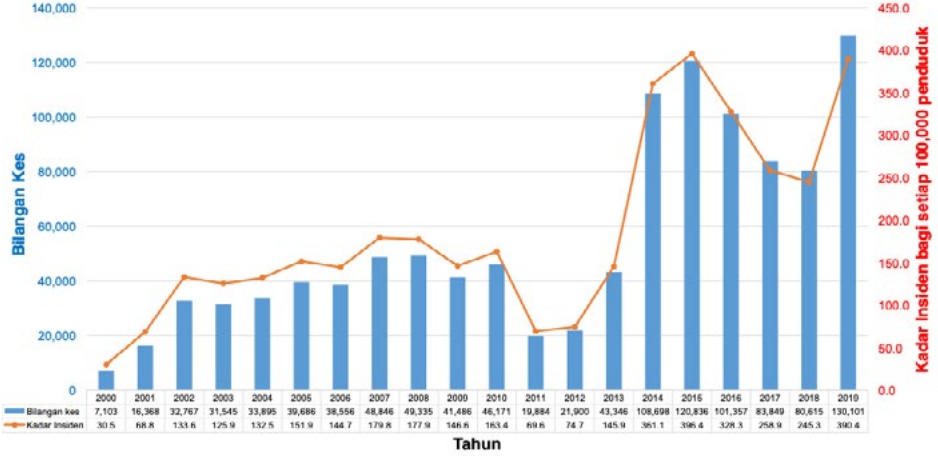
Clinical manifestations range from mild febrile illness to severe dengue manifested by plasma leakage, haemorrhagic tendencies, organ failure, shock, and possibly death. Fatality rates are around 0.1% to 1% in hospitalised cases. Prevention and control are based on mosquito vector control programmes and treatment is limited to supportive care. Vaccination represents a major opportunity to control dengue. Vaccination would be a part of an integrated approach in the fight against dengue, with strategies including vector control, environmental management and best clinical practices.

The majority of people living in high endemic areas have been infected by dengue by the time they reach adolescence. About 75% of dengue infections could be asymptomatic so most people may not know they had a previous dengue infection. For people who have had a previous dengue infection, vaccination should confer strong and persistent protection against dengue hospitalisations and severe disease.

Currently there are no WHO pre-qualified vaccines against dengue.

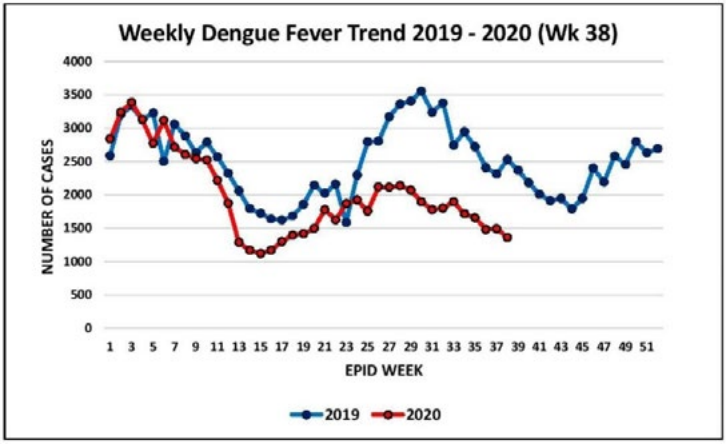
Figure 20.4.1
Dengue cases and deaths in Malaysia (2000-2019)

Dengue Cases and Deaths in Malaysia (2000-2019)



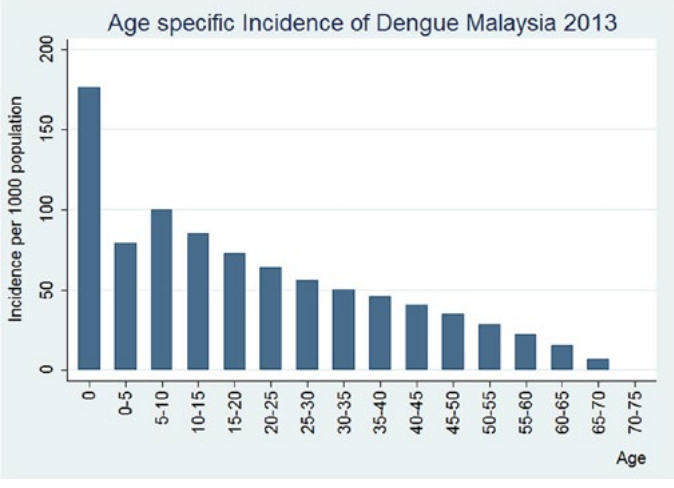
Source: https://idengue.mysa.gov.my/ide_v3/pdf/statistik.pdf#page=3

Figure 20.4.2
Dengue cases reported weekly in 2019 and 2020, Ministry of Health, Malaysia



Source: https://www.who.int/docs/default-source/wpro---documents/emergency/surveillance/dengue/dengue-20200924.pdf?sfvrsn=fc80101d_40

Figure 20.4.3
Age-specific dengue incidence rate per 1000 population, Malaysia, Year 2013



Source: Woon YL et al. "Estimating dengue incidence and hospitalization in Malaysia, 2001 to 2013." BMC Public Health (2018). 2018;18(1):946.

Upcoming Vaccines

Vaccines

A dengue vaccine, Dengvaxia® (CYD-TDV), was developed by Sanofi Pasteur. CYD-TDV is a tetravalent live recombinant chimeric dengue vaccine, based on the yellow fever 17D backbone. It is given as a 3-dose series on a 0, 6 and 12 months schedule for individuals 9-45 years of age living in endemic areas. It was first licensed in Mexico in December 2015, and is now licensed in some countries for people age 9-45 years old, including neighbouring countries Singapore, Indonesia, and Thailand.

A retrospective analysis of data from clinical trials using a newly developed NS1-based antibody assay, became available in November 2017. The findings showed that the vaccine raises the risk for severe dengue and hospitalisation in people with no prior exposure to the virus (seronegative vaccine recipients) compared to seronegative non-vaccinated individuals, while confirming long-term protection in seropositive individuals. The relative risk of getting severe dengue from a mosquito bite post-vaccination for a study participant 9 years of age or older who had no prior infection was similar to that seen in an unvaccinated person who gets a secondary infection. The findings also confirm the vaccine's population-level benefit and potential to prevent dengue, particularly severe dengue (84%) and hospitalisations due to dengue (80%) for the 5-year follow-up period of the study in individuals 9 years of age or older who have had a prior dengue infection. An update to the prescribing information was issued for the vaccine, recommending use in individuals with prior dengue infection and warning against vaccination of those without prior infection.

The Philippines is among the countries, including Mexico, El Salvador, Brazil, Singapore and Costa Rica, where CYD-TDV has been approved for marketing. Philippines had vaccinated more than 800,000 children with CYD-TDV since 2016 when it became the first country to start using it on a mass scale. CYD-TDV has been granted priority review by the FDA. In May 2019, FDA approved Dengvaxia® CYD-TDV for the prevention of dengue disease caused by all dengue virus serotypes (1, 2, 3 and 4) in people ages 9 through 16 who have

laboratory-confirmed previous dengue infection and who live in endemic areas.

About five other dengue vaccine candidates are in clinical development, with two candidates (developed by Takeda and NIH/Butantan) now in Phase 3 trials. The candidate dengue vaccines in development include recombinant, live attenuated, inactivated, DNA and viral-vector vaccines.

1. TAK-003 or DENVax

TAK-003 or DENVax is a recombinant chimeric tetravalent vaccine originally developed at Mahidol University in Bangkok and now funded by Takeda (TAK-003) and Inviragen (DENVax). TAK-003 is based on a live-attenuated DENV2 PDK53 (dengue virus type 2, passaged 53 times in primary dog kidney cells), which provides the genetic "backbone" for all four vaccine viruses, i.e. chimeric DENV1, DENV3 and DENV4 components on DENV2 backbone.

Phase 1 and 2 trials were conducted in the United States, Colombia, Puerto Rico, Singapore and Thailand. Based on 18-month data published earlier, TAK-003 produced sustained antibody responses against all four dengue serotypes, regardless of previous dengue exposure (both seropositive and seronegative participants) and dosing schedule. In the phase 2 randomized, placebo-controlled trial published in July 2020, TAK-003 was reported to be safe and well tolerated, and persistence of neutralizing antibody titers were demonstrated over 3 years in children and adults living in dengue-endemic countries. Seropositivity rates were 97.3%, 98.7%, 88% and 56% for DENV-1, -2, -3 and -4, respectively.

In January 2019, Takeda announced TAK-003 had met the primary endpoint in a pivotal Phase 3 clinical trial being conducted in Latin America (Brazil, Colombia, Dominican Republic, Nicaragua and Panama) and Asia (Philippines, Sri Lanka and Thailand). TAK-003 was found to be efficacious

in children and adolescents living in dengue-endemic countries, in preventing symptomatic dengue of any severity caused by any of the four dengue virus serotypes up to 15 months after administration of the first vaccine dose. TAK-003 is not yet licensed anywhere in the world.

2. TDENV PIV

TDENV PIV is a tetravalent purified inactivated vaccine undergoing phase I trials as part of a collaboration between GSK and the Walter Reed Army Institute of Research (WRAIR). A prime-boost strategy (synergistic formulation with another live attenuated candidate vaccine) is under evaluation in a phase II trial. In prime-boosting, one type of vaccine is followed by a boost with another type in an attempt to improve immunogenicity.

3. V180

V180 is a recombinant subunit vaccines by Merck, expressed in Drosophila S2 cells. Studies are in phase I stage in 2015.

4. D1ME100

The Naval Medical Research Center (NMRC) developed a monovalent plasmid DNA vaccine, D1ME100, but results in phase 1 proof-of-concept trial showed it to be only moderately immunogenic.

5. TetraVax-DV

TetraVax-DV is a live attenuated (recombinant) tetravalent vaccines, admixture of monovalent vaccines developed by the National Institute of Allergy and Infectious Diseases, National Institues of Health (NIAID). Several monovalent vaccines were tested separately for safety and immunogenicity. TV003 and TV005 candidate vaccines completed phase 1 trials and are being tested in phase 2 studies in Thailand and Brazil. In Brazil, the phase 2 studies are being done in collaboration with the Butantan Institute.

6. Other vaccines by manufacturers in India and Vietnam

Panacea Biotec and Biological E. Limited have vaccine candidates in the earliest stages of development. A company in Vietnam (Vabiotech) is conducting safety tests and developing a clinical trial plan. All three companies are involved in studies of a TetraVax-DV vaccine in conjunction with the National Institutes of Health (NIH).

Vaccines Available in Malaysia

There are no dengue vaccines available currently. In Malaysia, Dengvaxia® (CYD-TDV) was approved for conditional registration in April 2017, for a post-registration (Phase IV) clinical study for two years involving volunteers aged 9-45. These followed evaluation results in two Phase 3 clinical trials (CYD14 in five countries in Asia and CYD15 in five countries in Latin America).

The approval was given for the vaccine to be used in Phase IV clinical trials to get more information on vaccine safety, in which Sanofi Pasteur has to meet seven conditions before the product can be registered in Malaysia. However, the product did not fulfil all the stipulated conditions within the conditional registration period and hence, the registration was not continued.

Mode of Administration

- CYD-TDV is recommended as a 3-dose series given over a 12-month period (months 0, 6 and 12), by subcutaneous administration.
- Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered as soon as possible.

Contraindications And Adverse Effects

- The manufacturer stipulates that vaccination is contraindicated in:
  - » individuals with a history of severe allergic reaction to any component of the dengue vaccine or after prior administration of the dengue vaccine or a vaccine containing the same components.
  - » individuals with congenital or acquired immune deficiency that impairs cell-mediated immunity.
  - » individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.
  - » pregnant or breastfeeding women.
- CYD-TDV is not recommended in pregnant and lactating women because insufficient data are available on the use in pregnancy and lactation. However, no evidence of increased adverse pregnancy outcomes has been identified in the limited data generated from inadvertent vaccination of pregnant women that occurred during clinical trials.
- CYD-TDV is contraindicated in immunocompromised individuals due to lack of data.

Current status

- The Strategic Advisory Group of Experts (SAGE) on Immunization issued an updated recommendation on Dengvaxia® vaccine in April 2018, and the WHO Position Paper was published in September 2018, for countries considering vaccination as part of dengue control strategy.
- Dengue vaccination should be considered as part of an integrated strategy for dengue prevention and control. In countries or areas with high burden

disease, vaccination should only be recommended when the potential benefits outweigh the potential risks, and between population-level benefit versus individual-level risk.

- The likelihood of prior dengue infection in an individual before vaccination needs to be evaluated, and measures to minimise the risks among seronegative persons, where seronegative persons should not be vaccinated.

- The challenge is how to use the currently available CYD-TDV to maximise the public health impact, minimize harm and restore public confidence in dengue vaccines. Two main strategies are to be recommended for the vaccine to be further used in public programs:

  i. Pre-vaccination screening and vaccinating only those tested seropositive based on a screening test, or in some cases based on a documented laboratory-confirmed dengue infection in the past. This strategy is the preferred option, and may also be considered in low to moderate transmission settings, or

  ii. Subnational or national mass vaccination strategy based on population seroprevalence criteria, without individual pre-vaccination screening, for areas of high dengue burden i.e. areas with recent documentation of seroprevalence rates of at least 80% by age 9 years.

- These two approaches have limitations, for different reasons and with different implications, and achieving high population protection from dengue remains a challenge.

  i. Implementation of a pre-vaccination screening strategy with the currently available tests will require careful assessment, including consideration of the sensitivity and specificity of the tests and dengue epidemiology, country-specific dengue hospitalization rates, logistics issues and affordability of both screening tests and CYD-TDV.

ii. Screening tests would need to be highly specific to avoid vaccinating truly seronegative persons and to have high sensitivity to ensure that a high proportion of seropositive persons are vaccinated.

iii. Implementation of a seroprevalence criterion without individual screening will require serological surveys and mapping at high resolution, i.e. at district and sub-district level, to identify subnational areas with high disease burden or high seropositivity rates.

iv. Communication needs to ensure appropriate and full disclosure of:

- the limitations of the screening test to those offered vaccination.
- the risks of vaccination of persons with unknown serostatus.

- The optimal age group to be targeted is the age before severe dengue disease incidence is highest, which can be assessed from data such as the national and subnational routine hospital laboratory-confirmed surveillance data.
- Catch-up immunisation for other age-groups in areas with high disease burden may be necessary to control dengue. Disease-reporting data would be required to determine immunisation strategies and identify age groups for catch-up immunisations.
- There are currently no guidelines for dengue vaccination in travelers.
- HCWs are not at increased risk for dengue and they should follow the vaccine recommendations for adults based on age or other relevant risk factors.
- Research to be prioritised on the development of highly sensitive and specific, rapid screening tests to determine serostatus.
- Assessment of simplified immunization schedules and the need for booster doses should also be prioritized. There is currently no recommendation for a booster dose.

Evidence for Effectiveness

- Candidate vaccines in clinical trials appear to have acceptable short-term safety profiles. However, their long-term safety and duration of protection are yet to be confirmed. Severe disease due to vaccine failure and vaccine-induced immune enhancement of disease may be indistinguishable in individual vaccinees and benefit-risk assessments will have to rely on epidemiological studies. Both human host and viral factors could theoretically influence vaccine safety and merit careful evaluation in long-term safety assessments of dengue vaccines.

- Findings of the first phase 2b efficacy study in Thailand, of the Sanofi Pasteur CYD TDV was a major milestone which showed acceptable safety and neutralising antibody immunogenicity profile.

- The Asian Phase III trial (CYD14) evaluated the efficacy and safety of Sanofi's CYD TDV in 10,275 healthy children aged 2-14 years in Malaysia, Indonesia, the Philippines, Thailand and Vietnam. Results reported in July 2014 showed efficacy of 56.5% against virologically confirmed dengue as observed during 25 months of active surveillance. The data showed good serotype-specific protection, with better protection shown against DENV3 and DENV4 (75%). However, it showed less protection against DENV1 (50%) and least to DENV2 (35%). It is 88% effective against dengue haemorrhagic fever. Vaccine efficacy was statistically significant for all serotypes except DENV2 and vaccine safety was reassuring. The results also provided new insights in exploratory analyses, showing an increase in vaccine efficacy with age and a reduction of risk of severe disease in vaccinated children.

- The final landmark Phase III study (CYD15) conducted on 20,875 children aged 9-16 across 5 countries in Latin America – Brazil, Columbia, Honduras, Mexico and Puerta Rico was reported in September 2014. It confirmed that the vaccine was safe and provided high protection against dengue haemorrhagic fever. There was 80.3% lower risk of hospitalisation for dengue. Overall vaccine efficacy was 60.8%, and efficacy was observed against each of the 4 dengue serotypes. Efficacy was 42.3% against DENV2 compared to 35% in the Asian trial. As in the Asian trial, the vaccine was

more effective in people previously exposed to dengue, making the vaccine particularly useful in endemic areas.

- Together, these CYD14 and CYD15 trials included over 35,000 participants aged 2 to 16 years. Vaccine efficacy against confirmed dengue pooled across both trials was 59.2% in the year following the primary series (per protocol analysis). During this initial time period, pooled vaccine efficacy against severe dengue was 79.1%. Efficacy varied by serotype: vaccine efficacy was higher against serotypes 3 and 4 (71.6% and 76.9%, respectively) than for serotypes 1 and 2 (54.7% and 43.0%). Vaccine efficacy varied by age, dengue serotype, disease severity, and whether or not individuals had a previous natural dengue infection at vaccination. Vaccine efficacy against virologically confirmed dengue, over 25 month period from the first dose among 9-16 year-olds was 65.6% and in this age group severe dengue was reduced by 93% and hospitalisations with dengue by 82%.

- On 29 November 2017, Sanofi Pasteur announced the results of additional studies conducted to better describe the benefit-risk in seronegative individuals. A newly developed NS1-based antibody assay, which could distinguish prior vaccination from prior infection, was applied to serum samples taken 13 months after vaccination. This enabled the serostatus prior to vaccination to be inferred retrospectively, and enabled estimation of the efficacy and long-term safety of the vaccine by serostatus.

  » Overall population level benefit is favourable

  » CYD-TDV was found to perform differently in seropositive versus seronegative individuals. Vaccine efficacy (VE) against virologically-confirmed symptomatic dengue was high among inferred baseline seropositive participants aged 9 years or older: 76%, but much lower among baseline seronegative participants: 38.8% in the first 25 months after the first dose of vaccine.

  » In the approximate 5 year follow-up period after the first dose of vaccine, an overall higher risk of severe dengue and hospitalizations from dengue was observed in vaccinated seronegative trial participants of all ages compared to unvaccinated seronegative trial participants.

» Clinical manifestations and relative risk of severe dengue were similar in vaccinated seronegative persons compared to unvaccinated seropositive persons, consistent with the working hypothesis that CYD-TDV mimics a primary-like infection.

- Further data from Phase IV trials on CYD-TDV will provide further information for long-term duration of protection, vaccine safety and impact on dengue transmission, among other concerns.

- Takeda's TAK-003 vaccine was assessed in a double-blind, randomised and placebo-controlled Phase 3 trial, Tetravalent Immunisation against Dengue Efficacy Study (TIDES). This trial was designed to evaluate the efficacy, safety and immunogenicity of two doses of the vaccine. It is given subcutaneously three months apart in over 20,000 children and adolescents aged 4 to 16 years (both dengue exposed and naïve individuals) living in dengue-endemic areas, in Latin America and Asia.

  » The pivotal Phase 3 TIDES trial includes analysis on overall vaccine efficacy and assessment of secondary efficacy endpoints by serotype, baseline serostatus and disease severity (18 months after the second dose, which was administered three months after the first dose). Results demonstrated protection against virologically confirmed dengue (VCD) in children ages four to 16 years (overall efficacy was 73.3% [95% confidence interval (CI): 66.5% to 78.8%]. TAK-003 was generally well tolerated, and results were consistent with previously reported safety, immunogenicity and efficacy data for TAK-003.

  » Results of DEN-204 study, the phase 2 randomised, placebo-controlled trial of TAK-003 tetravalent dengue vaccine was published in the Lancet in March 2020. TAK-003 elicited antibody responses against all four serotypes, which persisted to 48 months post-vaccination, regardless of baseline serostatus. The results provide a long-term safety database and support further assessment of the vaccine in the ongoing phase 3 efficacy study. Further findings will help determine the potential utility of the Takeda vaccine as a tool in dengue prevention and form the basis for filing for licensure.

References

1. Bhatt, S., Gething, P. W., Brady, O. J., Messina, J. P., Farlow, A. W., Moyes, C. L., Drake, J. M., Brownstein, J. S., Hoen, A. G., Sankoh, O., Myers, M. F., George, D. B., Jaenisch, T., Wint, G. R., Simmons, C. P., Scott, T. W., Farrar, J. J., & Hay, S. I. (2013). The global distribution and burden of dengue. Nature, 496(7446), 504–507. https://doi.org/10.1038/nature12060
2. Biswal S, et al. HYPERLINK "https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30414-1/fulltext" Efficacy of a tetravalent dengue vaccine in health children aged 4-16 years: a randomized, placebo-controlled, phase 3 trial. Lancet. 2020. doi:10.1016/S0140-6736(20)30414-1.
3. Capeding, M. R., Tran, N. H., Hadinegoro, S. R., Ismail, H. I., Chotpitayasunondh, T., Chua, M. N., Luong, C. Q., Rusmil, K., Wirawan, D. N., Nallusamy, R., Pitisuttithum, P., Thisyakorn, U., Yoon, I. K., van der Vliet, D., Langevin, E., Laot, T., Hutagalung, Y., Frago, C., Boaz, M., Wartel, T. A., ... CYD14 Study Group (2014). Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet (London, England), 384(9951), 1358–1365. https://doi.org/10.1016/S0140-6736(14)61060-6
4. Coller, B. A., & Clements, D. E. (2011). Dengue vaccines: progress and challenges. Current opinion in immunology, 23(3), 391–398. https://doi.org/10.1016/j.coi.2011.03.005
5. Guy, B., Barrere, B., Malinowski, C., Saville, M., Teyssou, R., & Lang, J. (2011). From research to phase III: preclinical, industrial and clinical development of the Sanofi Pasteur tetravalent dengue vaccine. Vaccine, 29(42), 7229–7241. https://doi.org/10.1016/j.vaccine.2011.06.094
6. Hadinegoro, S. R., Arredondo-García, J. L., Capeding, M. R., Deseda, C., Chotpitayasunondh, T., Dietze, R., Muhammad Ismail, H. I., Reynales, H., Limkittikul, K., Rivera-Medina, D. M., Tran, H. N., Bouckenooghe, A., Chansinghakul, D., Cortés, M., Fanouillere, K., Forrat, R., Frago, C., Gailhardou, S., Jackson, N., Noriega, F., ... CYD-TDV Dengue Vaccine Working Group (2015). Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. The New England journal of medicine, 373(13), 1195–1206. https://doi.org/10.1056/NEJMoa1506223
7. L'Azou, M., Moureau, A., Sarti, E., Nealon, J., Zambrano, B., Wartel, T. A., Villar, L., Capeding, M. R., Ochiai, R. L., CYD14 Primary Study Group, & CYD15 Primary Study Group (2016). Symptomatic Dengue in Children in 10 Asian and Latin American Countries. The New England journal of medicine, 374(12), 1155–1166. https://doi.org/10.1056/NEJMoa1503877
8. McArthur, M. A., Sztein, M. B., & Edelman, R. (2013). Dengue vaccines: recent developments, ongoing challenges and current candidates. Expert review of vaccines, 12(8), 933–953. https://doi.org/10.1586/14760584.2013.815412
9. Mizumoto, K., Ejima, K., Yamamoto, T., & Nishiura, H. (2014). On the risk of severe dengue during secondary infection: a systematic review coupled with mathematical modeling. Journal of vector borne diseases, 51(3), 153–164.
10. Osorio, J. E., Wallace, D., & Stinchcomb, D. T. (2016). A recombinant, chimeric tetravalent dengue vaccine candidate based on a dengue virus serotype 2 backbone. Expert review of vaccines, 15(4), 497–508. https://doi.org/10.1586/14760584.2016.1128328
11. Sabchareon, A., Wallace, D., Sirivichayakul, C., Limkittikul, K., Chanthavanich, P., Suvannadabba, S., Jiwariyavej, V., Dulyachai, W., Pengsaa, K., Wartel, T. A., Moureau, A., Saville, M., Bouckenooghe, A., Viviani, S., Tornieporth, N. G., & Lang, J. (2012). Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet (London, England), 380(9853), 1559–1567. https://doi.org/10.1016/S0140-6736(12)61428-7
12. Sáez-Llorens, X., Tricou, V., Yu, D., Rivera, L., Jimeno, J., Villarreal, A. C., Dato, E., Mazara, S., Vargas, M., Brose, M., Rauscher, M., Tuboi, S., Borkowski, A., & Wallace, D. (2018). Immunogenicity and safety of one versus two doses of tetravalent dengue vaccine in healthy children aged 2-17 years in Asia and Latin America: 18-month interim data from a phase 2, randomised, placebo-controlled study. The Lancet. Infectious diseases, 18(2), 162–170. https://doi.org/10.1016/S1473-3099(17)30632-1
13. Sanofi Pasteur. (2017). Press release Sanofi updates information on dengue vaccine Available at: https://mediaroom.sanofi.com/ en/press-releases/2017/sanofi-updates-information-on-dengue-vaccine/ Accessed March 2019.
14. Schwartz, L. M., Halloran, M. E., Durbin, A. P., & Longini, I. M., Jr (2015). The dengue vaccine pipeline: Implications for the future of dengue control. Vaccine, 33(29), 3293–3298. https://doi.org/10.1016/j.vaccine.2015.05.010
15. Simmons, C. P., Farrar, J. J., Nguyen, v. V., & Wills, B. (2012). Dengue. The New England journal of medicine, 366(15), 1423–1432. https://doi.org/10.1056/NEJMra1110265

16. Sirivichayakul, C., Barranco-Santana, E. A., Rivera, I. E., Kilbury, J., Raanan, M., Borkowski, A., Papadimitriou, A., & Wallace, D. (2020). Long-term safety and immunogenicity of a tetravalent dengue vaccine candidate in children and adults: a randomized, placebo-controlled, phase 2 study. The Journal of infectious diseases, jiaa406. Advance online publication. https://doi.org/10.1093/infdis/jiaa406
17. Sridhar, S., Luedtke, A., Langevin, E., Zhu, M., Bonaparte, M., Machabert, T., Savarino, S., Zambrano, B., Moureau, A., Khromava, A., Moodie, Z., Westling, T., Mascareñas, C., Frago, C., Cortés, M., Chansinghakul, D., Noriega, F., Bouckenooghe, A., Chen, J., Ng, S. P., … DiazGranados, C. A. (2018). Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. The New England journal of medicine, 379(4), 327–340. https://doi.org/10.1056/NEJMoa1800820
18. The Ministry of Health, Malaysia (2020). Dengue cases and deaths in Malaysia (2000 – 2019). Available at https://idengue.mysa.gov.my/ide_v3/pdf/statistik.pdf#page=3 Accessed 10 October 2020.
19. Thomas, S.J., Endy, T.P. (2013). Current issues in dengue vaccination. Current Opinion in Infectious Diseases, 26(5): 429-34.
20. Tricou, V., Sáez-Llorens, X., Yu, D., Rivera, L., Jimeno, J., Villarreal, A. C., Dato, E., Saldaña de Suman, O., Montenegro, N., DeAntonio, R., Mazara, S., Vargas, M., Mendoza, D., Rauscher, M., Brose, M., Lefevre, I., Tuboi, S., Borkowski, A., & Wallace, D. (2020). Safety and immunogenicity of a tetravalent dengue vaccine in children aged 2-17 years: a randomised, placebo-controlled, phase 2 trial. Lancet (London, England), 395(10234), 1434–1443. https://doi.org/10.1016/S0140-6736(20)30556-0
21. Wallace, Derek; Canouet, Vincent; Garbes, Pedro; Wartel, T Anh. Challenges in the clinical development of a dengue vaccine. Curr Opin Immunol 2013; 3 (3): 352-6. https://doi.org/ HYPERLINK "https://doi.org/10.1097/01.qco.0000433310.28771.cc"10.1097/01.qco.0000433310.28771.cc
22. Whitehead S. S. (2016). Development of TV003/TV005, a single dose, highly immunogenic live attenuated dengue vaccine; what makes this vaccine different from the Sanofi-Pasteur CYD™ vaccine? Expert review of vaccines, 15(4), 509–517. https://doi.org/10.1586/14760584.2016.1115727
23. Woon, Y. L., Hor, C. P., Lee, K. Y., Mohd Anuar, S., Mudin, R. N., Sheikh Ahmad, M. K., Komari, S., Amin, F., Jamal, R., Chen, W. S., Goh, P. P., Yeap, L., Lim, Z. R., & Lim, T. O. (2018). Estimating dengue incidence and hospitalization in Malaysia, 2001 to 2013. BMC public health, 18(1), 946. https://doi.org/10.1186/s12889-018-5849-z
24. World Health Organisation (2009). Dengue: guidelines for diagnosis, treatment, prevention and control. WHO/HTM/NTD/ DEN/2009.1. Available at: http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf. Accessed March 2019.
25. World Health Organisation (2012). Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated) Annex 2. WHO Technical report series, No 979. Genève: Organisation mondiale de la Santé; 2013 (http://www.who.int/ biologicals/vaccines/Dengue_DB_5_April_2012_clean.pdf Accessed March 2019.
26. World Health Organisation (2018). Executive summary on dengue for SAGE. Available at: https://www.who.int/immunization/sage/meetings/2018/april/1_WHO_DengueExecSum_SAGE_Apr2018.pdf?ua=1 Accessed March 2019.
27. World Health Organization (2018). Dengue vaccine: WHO position paper – September 2018. Weekly Epidemiological Record. 93 (36): 457–476. Available at https://apps.who.int/iris/bitstream/handle/10665/274315/WER9336.pdf?ua=1. Accessed March 2019.
28. World Health Organization (2018). Fact sheet Dengue. Available at: http://www.who.int/news-room/fact-sheets/ detail/dengue-and-severe-dengue. Accessed March 2019.
29. World Health Organization (2019). Ten threats to global health in 2019. Available at: https://www.who.int/emergencies/tenthreats-to-global-health-in-2019. Accessed January 2019.
30. World Health Organization (2020). Dengue Situation Update Number 604. Available at https://www.who.int/docs/default-source/wpro---documents/emergency/surveillance/dengue/dengue-20200924.pdf?sfvrsn=fc80101d_40. Accessed October 2020.

Upcoming Vaccines

Ebola

Introduction

Ebola virus disease (EVD) is a severe illness in humans, with case fatality rate between 25% to 90%, with an average of about 50%. The virus is transmitted to human from wild animals and spreads through human-to-human transmission.

The first EVD outbreaks occurred in remote villages in Central Africa, near tropical rainforests. The 2014–2016 outbreak in West Africa was the largest and most complex Ebola outbreak since the virus was first discovered in 1976, involving major urban and rural areas. More than 28,000 cases and more than 11,000 deaths were recorded.

The second largest Ebola outbreak occurred in mid-2018, in a conflict-affected region of the Democratic Republic of the Congo (DRC). As of July 2020, more than 3400 cases were reported, with about 2300 deaths since the outbreak was declared on 1 August 2018.

There is no specific treatment for EVD. A range of potential treatments including blood products, immune therapies and drug therapies are currently under evaluation. The largest-ever Ebola vaccine campaign was a key factor in containing its spread. The introduction of two experimental vaccines involved inoculation of more than 320,000 people to date.

Vaccines

Twelve candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical development at different trial phases, and two have obtained approval.

1. rVSVΔG-ZEBOV-GP (Ervebo)

An rVSV-vectored candidate vaccine (rVSVΔG-ZEBOV-GP), consists of a vesicular stomatitis virus (VSV), which is an animal virus that causes flu-like illness in humans. The VSV has been genetically engineered to contain a protein from the Zaire Ebola virus so that it can induce an immune response to the Ebola virus.

The vaccine was studied in a Phase 3 trial involving 11,841 people during 2015. Among the 5,837 people who received the vaccine, no Ebola cases were recorded 10 days or more after vaccination. In comparison, there were 23 cases recorded 10 days or more after vaccination, among those who did not receive the vaccine. The trial was led by WHO, together with Guinea's Ministry of Health, Médecins sans Frontieres and other international collaborators. This is the only study that has reported clinical efficacy and effectiveness for a candidate Ebola vaccine, which was shown to be safe and protective against the Zaire strain of the Ebola virus. A single dose of rVSVΔG-ZEBOV-GP has shown 100% efficacy (95% confidence interval: 64–100%) in a cluster randomised 'ring vaccination' trial.

The rVSVΔG-ZEBOV-GP candidate vaccine is recommended by the Strategic Advisory Group of Experts on Immunisation (SAGE) for use in Ebola outbreaks caused by the Zaire strain of the virus, in the event where there is no licensed vaccine. It is being used under "expanded access" or what is also known as "compassionate use" in the Ebola outbreak in DRC which began in 2018. This vaccine was also used in the Ebola outbreak in Equateur in May-July 2018. In 2015, the vaccine was given to more than 16,000 volunteers involved in several studies in Africa, Europe and the United States where it was found to be safe and protective against the Ebola virus. More than 100,000 people have received the vaccine, by far the largest use of it since a trial in 2015 showed good efficacy. SAGE recommends vaccination of health care workers and frontline workers who may be in contact with Ebola patients.

For the protection of persons at highest risk of the Ebola outbreak, a 'ring vaccination' strategy is applied, which is similar to the approach used to eradicate smallpox. This strategy captures a social network of individuals and locations that may include dwellings or workplaces further afield, where the index patient spent time while symptomatic, or the households of individuals who had contact with the patient during the illness or after his or her death. Each 'ring' may be composed of an average of 150 persons:

i. Contacts, and contacts of contacts of confirmed Ebola virus disease patients (dead or alive),
ii. Health care and frontline workers (local and international) in the affected areas, and
iii. Health care and frontline workers in areas at risk of spread of the outbreak.

The rVSVΔG-ZEBOV-GP candidate vaccine was granted access to the Priority Medicine (PRIME) scheme by the European Medicine Agency (EMA), and Breakthrough Therapy designation by the US Food and Drug Administration (FDA). In November 2019, the European Commission granted a conditional marketing authorization to this vaccine (tradename "Ervebo") and the WHO prequalified an Ebola vaccine for the first time. The US FDA approved this Ebola vaccine in December 2019. The vaccine is a single dose vaccine regimen that has been found to be safe and protective against only the Zaire ebolavirus species of ebolavirus. This is the first approval of a vaccine for Ebola.

2. Ad26.ZEBOV & MVA-BN-Filo (VAC52150) (Zabdeno and Mvabea)

This vaccine (Johnson & Johnson, & Janssen Vaccines & Prevention B.V, The Netherlands) is a prime/ boost candidate vaccine consisting of Ad26- and MVA-vectored components. It is a non-replicative, recombinant adenovirus serotype 26 expressing envelope GP of Zaire Ebola virus species and modified vaccinia Ankara expressing 4 filoviruses nucleoproteins (GP for Zaire Ebola [Mayinga strain], Sudan Ebola, and

Marburg viruses and nucleoprotein of Taï Forest Ebola virus). Two doses are required; an initial dose followed by a second "booster" dose 56 days later. This vaccine is also designed to protect against only the Zaire ebolavirus species of Ebola.

In September 2019, the European Medicines Agency (EMA) granted an accelerated assessment and in November 2019, Janssen submitted a Marketing Authorization Application (MAA) to the EMA for approval. In May 2020, the EMA recommended granting a marketing authorization for the combination of Ad26.ZEBOV (Zabdeno) and MVA-BN-Filo (Mvabea) vaccines. The vaccine was approved for medical use in the European Union in July 2020.

3. GamEvac-Combi

A prime/boost candidate vaccine based on rVSV- and Ad5-vectored components (GamEvac-Combi) is registered Russia, its country of origin, based on Phase 2 data. It is a replicative, recombinant vesicular stomatitis virus and human adenovirus serotype 5 expressing envelope GP of Zaire (Makona strain) Ebola virus (prime & heterologous boost).

The rVSVΔG-ZEBOV-GP candidate vaccine and (Ad26.ZEBOV/MVA-BN-Filo) have been submitted for WHO Emergency Use Assessment and Listing (EUAL) documentation. More research is needed for the candidate vaccines, particularly on the duration of protection, and cross-protection against other species of Ebola virus and other filoviruses.

References

1. Centers for Disease Control and Prevention, US. Ebola (Ebola Virus Disease) Prevention and Vaccine. Available at https://www.cdc.gov/vhf/ebola/prevention/index.html. Accessed October 2020.
2. European Medicines Agency (EMA). (2020). New vaccine for prevention of Ebola virus disease recommended approval in the European Union. Press release 29 May 2020.
3. Geisbert, T. (2017). First Ebola virus vaccine to protect human beings? The Lancet, 389(10068), 479–480. https://doi.org/10.1016/S0140-6736(16)32618-6
4. Merck. (2019). Merck's Ervebo [Ebola Zaire Vaccine (rVSV- G-ZEBOV-GP) live] Granted Conditional Approval in the European Union. Press release November 2019. Available at https://www.businesswire.com/news/home/20191111005601/en/Merck%E2%80%99s-ERVEBO%C2%AE-Ebola-Zaire-Vaccine-rVSV%CE%94G-ZEBOV-GP-live
5. Trad, M. A., Naughton, W., Yeung, A., Mazlin, L., O'sullivan, M., Gilroy, N., Fisher, D. A., & Stuart, R. L. (2017). Ebola virus disease: An update on current prevention and management strategies. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology, 86, 5–13. https://doi.org/10.1016/j.jcv.2016.11.005
6. U.S. Food and Drug Administration (FDA). (2019). First FDA-approved vaccine for the prevention of Ebola virus disease, marking a critical milestone in public health preparedness and response. Press release 19 December 2019.
7. WHO Ebola Response Team, Agua-Agum, J., Allegranzi, B., Ariyarajah, A., Aylward, R., Blake, I. M., Barboza, P., Bausch, D., Brennan, R. J., Clement, P., Coffey, P., Cori, A., Donnelly, C. A., Dorigatti, I., Drury, P., Durski, K., Dye, C., Eckmanns, T., Ferguson, N. M., Fraser, C., ... Van Kerkhove, M. D. (2016). After Ebola in West Africa--Unpredictable Risks, Preventable Epidemics. The New England journal of medicine, 375(6), 587–596. https://doi.org/10.1056/NEJMsr1513109
8. WHO Fact Sheet: Ebola Virus Disease. Available at https://www.who.int/news-room/factsheets/detail/ebola-virus-disease. Accessed March 2019.
9. Meeting of the Strategic Advisory Group of Experts on immunization, April 2017 – conclusions and recommendations. (2017). Wkly Epidemiol Rec., 92(22), 301–320.
10. WHO Update With The Development Of Ebola Vaccines And Implications To Inform Future Policy Recommendations. Ebola vaccines - Background paper for SAGE deliberations. Available at https://www.who.int/immunization/sage/meetings/2017/april/1_Ebola_vaccine_background_document.pdf
11. World Health Organization. (2019). WHO prequalifies Ebola vaccine, paving the way for its use in high-risk countries. Press release 12 November 2019. https://www.who.int/news/item/12-11-2019-who-prequalifies-ebola-vaccine-paving-the-way-for-its-use-in-high-risk-countries. Accessed October 2020.

Enterovirus 71 (EV71)

Introduction

Enterovirus 71 (EV71) is a member of the Enterovirus genus of the Picornaviridae family. It is the second most common causative pathogens of hand-foot-and-mouth disease (HFMD), after coxsackievirus A16 (CVA16), and the most common aetiological agent isolated from HFMD patients complicated with neurological disorders. EV71 is an increasingly important neurotropic enterovirus in the post-polio eradication era. Although most HFMD do not result in serious complications, outbreaks of HFMD caused by EV71 can present with a high rate of neurological complications, including aseptic meningitis, encephalitis, acute flaccid paralysis, pulmonary complications, cardiovascular complications and fatal consequences.

HFMD is a major emerging infectious disease in Asia-Pacific region, with increasing incidence over the past 2 decades and of public health importance. Epidemics occur in countries including China, Taiwan, Singapore, Japan and Malaysia. Across South East Asia, HFMD affects approximately 2,000,000 children every year.

In Malaysia, since the initial enterovirus 71 (EV71) outbreak in Sarawak in 1997, data showed that EV71 outbreaks occur in a regular cyclical pattern every 3 years. In the 2006 outbreak, there were 14,000 cases with 13 deaths. All outbreaks documented (1997, 2000, 2003, and 2006) have been predominantly caused by EV71 of genogroup B. Outbreaks of HFMD were also reported in Peninsular Malaysia, where EV71 and CVA16 were the main aetiological viruses isolated and more than one sub-genogroup of EV71 co-circulate in the past outbreaks in the country. In 2018, HFMD soared to near epidemic levels with over 55,000 cases, with the outbreak in Penang involving more than 3,700 cases.

EV71 virus is divided into 3 genotypes on the basis of VP1 sequence: A, B, and C, then into 11 sub-genotypes. Some viral sub-genotypes seem to have great potential for epidemics, whereas others have more-indolent, low-level circulation. C4 is the most prevalent EV71 genotype found in China, Hong Kong, Korea, and Vietnam, whereas B5 is the most common genotype circulating in Japan, Malaysia, and Taiwan.

The virus is transmitted through direct contact with nasopharyngeal secretions, saliva, fluid from blisters, or stool of infected persons. Indirect transmission occurs through contaminated materials touched by an infected person. Patients are infectious during the stage when they have high fever. Several antiviral strategies are under investigation, including small molecules and antibodies.

Vaccines

Several reviews on EV71 vaccine development have been published. Since morbidity and mortality from EV71 infection is low, the major effect of this vaccine will be to reduce hospital admissions. EV71 vaccines being developed and at various stages of clinical trials include:

i. Inactivated whole-virus

ii. Live attenuated virus

iii. Virus-like particles

iv. DNA vaccines and recombinant vector vaccines

v. Recombinant proteins and synthetic peptides

Five organisations have completed pre-clinical studies focused on the development of inactivated EV71 whole-virus vaccines, including vaccine strain screening, process optimisation, safety and immunogenicity evaluation,

and are in different stages of clinical trials. Three of these are companies in mainland China (Institute of Medical Biology, Chinese Academy of Medical Science (CAMS), Sinovac Biotech Co. Ltd. and Beijing Vigoo Biological Co. Ltd.), that have successfully completed phase III randomised, double-blinded, placebo controlled trials. These Phase III clinical trials have involved more than 30,000 infants and children. All three vaccines are inactivated whole-virus alum-adjuvant vaccines that use C4 genotype virus strain.

China Food and Drug Administration (CFDA) has approved the three EV71 vaccines against HFMD in children. The first vaccine approval was in 2015 for CAMS vaccine candidate, followed by the second vaccine made by Sinovac Biotech in 2016.

Two other formalin-inactivated whole-virus vaccines, developed by the National Health Research Institutes (NHRI) of Taiwan and Inviragen of Singapore, have also completed Phase I clinical trials. The results of clinical trials suggest a promising future for the clinical use of EV71 vaccines.

Monitoring for epidemiological variations in EV71 will be necessary to determine whether the vaccine has ongoing, long-term efficacy and detection of any genogroup replacement. The next step would be development of bivalent or multivalent vaccines, to protect against other common HFMD pathogens including CVA16.

Vaccines Available in Malaysia

Currently no vaccine is registered.

Mode of Administration

Intramuscular administration and various dosage regimens are being assessed in clinical trials.

Target Groups in Malaysia

When available, the probable target population for vaccination would be young children especially those under 3 years, who are the most susceptible to severe disease.

Evidence for Effectiveness

A multicentre randomised controlled trial done in China demonstrated vaccine protection against EV71. This trial included more than 10,000 children (aged 6–35 months), showed vaccine efficacy of 90.0% for EV71-associated HFMD and 80.4% for EV71-associated disease (including herpangina, neurological complications, and non-specific illnesses caused by EV71). Safety profile was satisfactory and the results are similar to those for inactivated poliovirus vaccine.

References

1. Chua, K. B., & Kasri, A. R. (2011). Hand foot and mouth disease due to enterovirus 71 in Malaysia. Virologica Sinica, 26(4), 221–228. https://doi.org/10.1007/s12250-011-3195-8
2. Crawford, N. W., & Graham, S. M. (2013). EV71 vaccine: protection from a previously neglected disease. Lancet (London, England), 381(9882), 1968–1970. https://doi.org/10.1016/S0140-6736(13)61124-1
3. Kuo, R. L., & Shih, S. R. (2013). Strategies to develop antivirals against enterovirus 71. Virology journal, 10, 28. https://doi.org/10.1186/1743-422X-10-28
4. Li, R., Liu, L., Mo, Z., Wang, X., Xia, J., Liang, Z., Zhang, Y., Li, Y., Mao, Q., Wang, J., Jiang, L., Dong, C., Che, Y., Huang, T., Jiang, Z., Xie, Z., Wang, L., Liao, Y., Liang, Y., Nong, Y., ... Li, Q. (2014). An inactivated enterovirus 71 vaccine in healthy children. The New England journal of medicine, 370(9), 829–837. https://doi.org/10.1056/NEJMoa1303224
5. Li, Y.P., Liang, Z.L., Xia, J.L., Wu, J.Y., Wang, L., Song, L.F., Mao, Q.Y., et al. (2013). Immunogenicity, Safety, and Immune persistence of A Novel Inactivated Human Enterovirus 71 (EV71) Vaccine: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial, The Journal of Infectious Diseases, Volume 209, 46–55, https://doi.org/10.1093/infdis/jit429
6. Liang, Z. L., Mao, Q. Y., Wang, Y. P., Zhu, F. C., Li, J. X., Yao, X., Gao, F., Wu, X., Xu, M., & Wang, J. Z. (2013). Progress on the research and development of inactivated EV71 whole-virus vaccines. Human vaccines & immunotherapeutics, 9(8), 1701–1705. https://doi.org/10.4161/hv.24949
7. Liang, Z., Mao, Q., Gao, F., & Wang, J. (2013). Progress on the research and development of human enterovirus 71 (EV71) vaccines. Frontiers of medicine, 7(1), 111–121. https://doi.org/10.1007/s11684-012-0237-z
8. Ooi, M. H., Wong, S. C., Lewthwaite, P., Cardosa, M. J., & Solomon, T. (2010). Clinical features, diagnosis, and management of enterovirus 71. The Lancet. Neurology, 9(11), 1097–1105. https://doi.org/10.1016/S1474-4422(10)70209-X
9. Podin, Y., Gias, E. L., Ong, F., Leong, Y. W., Yee, S. F., Yusof, M. A., Perera, D., Teo, B., Wee, T. Y., Yao, S. C., Yao, S. K., Kiyu, A., Arif, M. T., & Cardosa, M. J. (2006). Sentinel surveillance for human enterovirus 71 in Sarawak, Malaysia: lessons from the first 7 years. BMC public health, 6, 180. https://doi.org/10.1186/1471-2458-6-180
10. Reed, Z., & Cardosa, M. J. (2016). Status of research and development of vaccines for enterovirus 71. Vaccine, 34(26), 2967–2970. https://doi.org/10.1016/j.vaccine.2016.02.077
11. Solomon, T., Lewthwaite, P., Perera, D., Cardosa, M. J., McMinn, P., & Ooi, M. H. (2010). Virology, epidemiology, pathogenesis, and control of enterovirus 71. The Lancet. Infectious diseases, 10(11), 778–790. https://doi.org/10.1016/S1473-3099(10)70194-8
12. Xu, J., Qian, Y., Wang, S., Serrano, J. M., Li, W., Huang, Z., & Lu, S. (2010). EV71: an emerging infectious disease vaccine target in the Far East?. Vaccine, 28(20), 3516–3521. https://doi.org/10.1016/j.vaccine.2010.03.003
13. Zhang, D., Lu, J., & Lu, J. (2010). Enterovirus 71 vaccine: close but still far. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases, 14(9), e739–e743. https://doi.org/10.1016/j.ijid.2009.12.002
14. Zhu, F. C., Meng, F. Y., Li, J. X., Li, X. L., Mao, Q. Y., Tao, H., Zhang, Y. T., Yao, X., Chu, K., Chen, Q. H., Hu, Y. M., Wu, X., Liu, P., Zhu, L. Y., Gao, F., Jin, H., Chen, Y. J., Dong, Y. Y., Liang, Y. C., Shi, N. M., ... Shen, X. L. (2013). Efficacy, safety, and immunology of an inactivated alum-adjuvant enterovirus 71 vaccine in children in China: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England), 381(9882), 2024–2032. https://doi.org/10.1016/S0140-6736(13)61049-1

Upcoming Vaccines

Human Immunodeficiency Virus (HIV)

Introduction

Since the start of the epidemic in 1980s, more than 70 million people have been infected with HIV and AIDS-related death toll of about 35 million. Sub-Saharan Africa is the region most impacted by the virus, with one out of every 25 adults living with HIV (WHO). In Malaysia, the cumulative number of reported HIV cases is 118,883; the cumulative number of reported AIDS 25,925; while the total number of deaths related to HIV/AIDS is 43,843. At the end of year 2018, it is estimated that 87,041 people living with HIV (PLHIV) in Malaysia, 75,040 of whom were notified through the national surveillance system. About 55% of the reported PLHIV were receiving antiretroviral treatment. More than 70% of HIV new infections are reported among people aged 20 to 39 years, while children aged less than 13 years old are approximately less than 1%.

Since 1987, more than 30 HIV candidate vaccines have been tested in approximately 60 Phase I/II trials, involving more than 10,000 healthy volunteers. Most of these trials have been conducted in the United States and Europe, but several have also been conducted in developing countries (Brazil, China, Cuba, Haiti, Kenya, Peru, Thailand, Trinidad, and Uganda). The results have confirmed the safety of the vaccines, and have provided important scientific information to develop newer generations of candidate vaccines with better ability to induce anti-HIV specific immune responses.

Vaccines

Currently no vaccine is registered. A preventive HIV vaccine is given to people who do not have HIV. There have been no passive preventive HIV vaccines to reach Phase III yet, but some active preventive HIV vaccine candidates have entered Phase III.

RV144 vaccine candidate is a prime-boost combination of two vaccine components (AIDSVAX B/E and ALVAC), given in sequence: one using recombinant canary pox as a vector or carrier to deliver HIV genes and a second containing gp120 protein found on the HIV surface. The RV144 trial in Thailand showed partial efficacy in preventing HIV.

In 2016, the phase IIb-III trial HVTN 702 / "Uhambo" was launched in South Africa, aiming to build on the RV144 results. HVTN 702 tests a new version of RV144 vaccines, adapted for the subtype of HIV common to the sub-Saharan Africa region, where most new HIV infections occur. The trial vaccines are the ALVAC vector vaccine and a two-component gp120 protein subunit vaccine with MF59 adjuvant. HVTN 702 study led by South African researchers, tests efficacy in preventing HIV infection in adults. Results of this vaccine efficacy trial are expected in late 2020.

A therapeutic HIV vaccine is given to a person who already has HIV, designed to improve the body's immune response to HIV. The use of therapeutic HIV vaccines is being explored, with goals including:

- to slow down the progression of HIV infection
- to eliminate the need for antiretroviral therapy (ART) while still keeping undetectable levels of HIV
- as part of a larger strategy to eliminate all HIV from the body

Current therapeutic HIV vaccine approaches:

- Inactivated whole virus depleted of gp120
- Single or multiple HIV antigens administered as DNA
- Autologous Dendritic Cells
- Viral vectors e.g. poxviruses (canarypox ALVAC-HIV, vCP1452, vCP1433, fowlpox, MVA), adenoviruses (Ad5)

Evidence for Effectiveness

- The landmark RV144 Phase 3 clinical trial in Thailand involved 16,395 participants, which evaluated safety and efficacy. Results from this were reported in 2009. The vaccine showed modest efficacy in reducing HIV infection among vaccinees.

  In this trial, 8197 of participants were given treatment consisting of two experimental vaccines targeting HIV types B and E that are prevalent in Thailand, while 8198 were given a placebo. The participants were tested for HIV every six months for three years. After three years, the vaccine group saw HIV infection rates reduced by about 30% compared with those in the placebo group.

- Tat therapeutic vaccine, developed by The Italian National AIDS Center, targets HIV-1 transactivator of transcription (Tat) protein. Phase 2 trial of Tat showed statistically significant reduction of blood HIV-1 DNA load that persisted for up to three years post-vaccination.

- Broadly neutralising antibodies, or bNAbs, can prevent many HIV strains from infecting human cells in the laboratory. Researchers have isolated bNAbs from the blood of people living with HIV and studying them in an effort to design novel vaccine candidates. VRC01 is a human monoclonal antibody targeting HIV-1 CD4 binding site. Early-phase clinical trials of VRC01 and another human monoclonal antibody, 3BNC117, showed reduced viral load in HIV-1-infected individuals not on HAART. HVTN 703 and HTVN 704 trials investigate the effectiveness of VRC01. The results of both studies are expected in 2022.

References

1. Ensoli, F., Cafaro, A., Casabianca, A., Tripiciano, A., Bellino, S., Longo, O., Francavilla, V., Picconi, O., Sgadari, C., Moretti, S., Cossut, M. R., Arancio, A., Orlandi, C., Sernicola, L., Maggiorella, M. T., Paniccia, G., Mussini, C., Lazzarin, A., Sighinolfi, L., Palamara, G., ... Ensoli, B. (2015). HIV-1 Tat immunization restores immune homeostasis and attacks the HAART-resistant blood HIV DNA: results of a randomized phase II exploratory clinical trial. Retrovirology, 12, 33. https://doi.org/10.1186/s12977-015-0151-y
2. Gray, G. E., Laher, F., Doherty, T., Abdool Karim, S., Hammer, S., Mascola, J., Beyrer, C., & Corey, L. (2016). Which New Health Technologies Do We Need to Achieve an End to HIV/AIDS?. PLoS biology, 14(3), e1002372. https://doi.org/10.1371/journal.pbio.1002372
3. Gray, G. E., Laher, F., Lazarus, E., Ensoli, B., & Corey, L. (2016). Approaches to preventative and therapeutic HIV vaccines. Current opinion in virology, 17, 104–109. https://doi.org/10.1016/j.coviro.2016.02.010
4. Hammer, S. M., Sobieszczyk, M. E., Janes, H., Karuna, S. T., Mulligan, M. J., Grove, D., Koblin, B. A., Buchbinder, S. P., Keefer, M. C., Tomaras, G. D., Frahm, N., Hural, J., Anude, C., Graham, B. S., Enama, M. E., Adams, E., DeJesus, E., Novak, R. M., Frank, I., Bentley, C., ... HVTN 505 Study Team (2013). Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. The New England journal of medicine, 369(22), 2083–2092. https://doi.org/10.1056/NEJMoa1310566
5. Lynch, R. M., Boritz, E., Coates, E. E., DeZure, A., Madden, P., Costner, P., Enama, M. E., Plummer, S., Holman, L., Hendel, C. S., Gordon, I., Casazza, J., Conan-Cibotti, M., Migueles, S. A., Tressler, R., Bailer, R. T., McDermott, A., Narpala, S., O'Dell, S., ... Ledgerwood, J. E. (2015). Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. Science Translational Medicine, 7(319), 319ra206. https://doi.org/10.1126/scitranslmed.aad5752
6. National Institute of Allergy and Infectious Diseases. History of HIV Vaccine Research. Available at https://www.niaid.nih.gov/diseases-conditions/hiv-vaccine-research-history. Accessed August 2020.
7. Rerks-Ngarm, S., Pitisuttithum, P., Nitayaphan, S., Kaewkungwal, J., Chiu, J., Paris, R., Premsri, N., Namwat, C., de Souza, M., Adams, E., Benenson, M., Gurunathan, S., Tartaglia, J., McNeil, J. G., Francis, D. P., Stablein, D., Birx, D. L., Chunsuttiwat, S., Khamboonruang, C., Thongcharoen, P., ... MOPH-TAVEG Investigators (2009). Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. The New England journal of medicine, 361(23), 2209–2220. https://doi.org/10.1056/NEJMoa0908492
8. The Ministry of Heath Malaysia. (2019). Country Progress Report on HIV/AIDS 2019 – Malaysia. Available at https://www.moh.gov.my/moh/resources/Penerbitan/Laporan/Umum/Report_GAM_2019_(Final).pdf. Accessed October 2020.
9. Xu, K., Acharya, P., Kong, R., Cheng, C., Chuang, G. Y., Liu, K., Louder, M. K., O'Dell, S., Rawi, R., Sastry, M., Shen, C. H., Zhang, B., Zhou, T., Asokan, M., Bailer, R. T., Chambers, M., Chen, X., Choi, C. W., Dandey, V. P., Doria-Rose, N. A., ... Kwong, P. D. (2018). Epitope-based vaccine design yields fusion peptide-directed antibodies that neutralize diverse strains of HIV-1. Nature medicine, 24(6), 857–867. https://doi.org/10.1038/s41591-018-0042-6

Upcoming Vaccines

Malaria

Introduction

An estimated 216 million cases of malaria occurred worldwide, leading to an estimated 445,000 deaths in 2016 (WHO). Children under the age of five in sub-Saharan Africa are especially vulnerable, accounting for approximately two thirds of all global deaths due to malaria. *Plasmodium falciparum* is the most prevalent malaria parasite in sub-Saharan Africa, accounting for 99% of estimated malaria cases in 2016.

In Malaysia, malaria risk exists in limited foci in the states of Sabah and Sarawak and the central areas of Peninsular Malaysia. The risk is present in the mountainous interiors of the states of Kedah, Perak, Kelantan Pahang, Selangor and Negeri Sembilan. Urban and coastal areas of peninsular Malaysia, including the island of Penang are risk free.

Malaysia is very close to reaching the WHO target of human malaria elimination. MOH has targeted Malaysia to be declared a human indigenous malaria free nation by the WHO by 2020. In 2017, only 85 people were infected with human malaria. With the Malaria Elimination Programme in place, malaria cases decreased from 4,164 in 2011 to zero cases in 2018. However, since 2008, Malaysia has reported more than 15,000 cases of *P. knowlesi* infection and about 50 deaths. Infections in 2017 alone totalled 3,600. The risk of *P. knowlesi* infection, which is now known as the fifth human malaria species, is closely tied to rapid deforestation. *P. knowlesi* is increasingly reported elsewhere in Southeast Asia, including Indonesia, Thailand, Vietnam, and Myanmar. There is currently no vaccine against *P. knowlesi* in the pipeline. The human malaria vaccine does not protect against *P. knowlesi* malaria.

Vaccines

Currently no vaccine against human malaria is registered. More than 20 vaccine candidates are currently being evaluated in clinical trials or in advanced preclinical phases. Various vaccine concepts for human malaria vaccine candidates include:

i. Sporozoite subunit vaccines: pre-erythrocytic vaccines that prevent infection

ii. Whole sporozoite vaccines

iii. Liver-stage subunit vaccines

iv. Blood-stage vaccines: limit infection and disease

v. Transmission-blocking vaccines: interrupt the spread of infection

Recent progress has been made with the completion of a Phase 3 trial of the RTS,S/AS01 candidate vaccine and review by the European Medicines Agency and WHO. The RTS,S/AS01 (commercial name Mosquirix), a sporozoite subunit vaccine, is currently at Phase 4 trial. It targets the CS protein on the sporozoite of *P. falciparum*. It is a combination of CS protein (PfCSP), hepatitis B surface antigen, and AS01 adjuvant which create a more robust immune response than nature.

The Phase 3 trial of RTS,S/AS01 was conducted over 5 years (2009–2014) in 11 sites in 7 sub-Saharan African countries: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and the United Republic of Tanzania. The trial enrolled approximately 15,500 infants and young children, and showed protective efficacy against clinical malaria. Two safety signals (meningitis, cerebral malaria) were recorded, for which the cause is unknown and a confirmed risk of febrile convulsions within 7 days of vaccination was noted in the 5–17 month age category, all of which resolved without long-term sequelae.

Upcoming Vaccines

In January 2016, WHO published its position paper for this first malaria vaccine, officially adopting the joint recommendation by SAGE and the Malaria Policy Advisory Committee (MPAC). WHO recommends pilot implementation of vaccine in selected areas in sub-Saharan Africa in order to generate critical evidence for potential wider scale application. Three countries (Ghana, Kenya, Malawi) were selected to participate in pilot program called the Malaria Vaccine Implementation Program (MVIP), to be implemented from 2017 to 2022. The MVIP aims to support the introduction of the vaccine through routine immunisation program and to evaluate the outstanding questions related to the public health use of the vaccine. Preparatory work for regulatory approval, vaccine introduction and pilot evaluation has been initiated. The MVIP consists of three components:

1. **Vaccine introduction:** National immunisation programmes in Ghana, Kenya, and Malawi will lead the pilot introduction of the malaria vaccine in areas with moderate to high malaria transmission.

2. **Pilot evaluation:** A master protocol has been developed to evaluate:

i. the programmatic feasibility of delivering RTS,S/AS01 with new immunisation contacts, including the fourth dose in the second year of life;

ii. the vaccine's impact on mortality and

iii. the vaccine's safety in the context of routine immunisation, with an emphasis on meningitis and cerebral malaria.

3. **GSK Phase 4 study:** The GSK-sponsored observational Phase 4 studies to further assess vaccine safety, effectiveness and impact in routine use. The WHO-led pilot evaluation has been designed to complement the GSK Phase 4 study that will take place in a small sub-set of the pilot areas.

   Another candidate malaria vaccine is the PfSPZ vaccine developed by Sanaria. It is made of non-replicating irradiated whole sporozoites and and also targets pre-erythrocytic stage of the parasite. It was granted fast track designation by the U.S. Food and Drug Administration in September 2016.

Evidence for Effectiveness

In the Phase 3 trial of RTS,S/AS01, among children aged 5–17 months who received three doses of vaccines administered at 1- month intervals, followed by a fourth dose 18 months later, the vaccine reduced malaria episodes by 39%, equivalent to preventing nearly 4 in 10 malaria cases. In addition, the 4-dose vaccine schedule reduced severe malaria by 32% in this age group, with reductions in malaria hospitalisations (37%), all-cause hospitalisation (15%) and severe anaemia (62%). Blood transfusions were reduced by 29%. The protective benefit against severe malaria was absent among children who did not receive the fourth dose.

Protection was found to be age-dependent, where vaccine efficacy was low in the younger (6–12 weeks) age category in this Phase 3 trial. Due to the low efficacy, the use of the vaccine in this age category is not recommended.

References

1. Barber, B. E., Rajahram, G. S., Grigg, M. J., William, T., & Anstey, N. M. (2017). World Malaria Report: time to acknowledge Plasmodium knowlesi malaria. Malaria journal, 16(1), 135. https://doi.org/10.1186/s12936-017-1787-y
2. Collins, K. A., Snaith, R., Cottingham, M. G., Gilbert, S. C., & Hill, A. (2017). Enhancing protective immunity to malaria with a highly immunogenic virus-like particle vaccine. Scientific reports, 7, 46621. https://doi.org/10.1038/srep46621
3. Draper, S. J., Sack, B. K., King, C. R., Nielsen, C. M., Rayner, J. C., Higgins, M. K., Long, C. A., & Seder, R. A. (2018). Malaria Vaccines: Recent Advances and New Horizons. Cell host & microbe, 24(1), 43–56. https://doi.org/10.1016/j.chom.2018.06.008
4. Fornace, K. M., Abidin, T. R., Alexander, N., Brock, P., Grigg, M. J., Murphy, A., William, T., Menon, J., Drakeley, C. J., & Cox, J. (2016). Association between Landscape Factors and Spatial Patterns of Plasmodium knowlesi Infections in Sabah, Malaysia. Emerging infectious diseases, 22(2), 201–208. https://doi.org/10.3201/eid2202.150656
5. Ishizuka, A. S., Lyke, K. E., DeZure, A., Berry, A. A., Richie, T. L., Mendoza, F. H., Enama, M. E., Gordon, I. J., Chang, L. J., Sarwar, U. N., Zephir, K. L., Holman, L. A., James, E. R., Billingsley, P. F., Gunasekera, A., Chakravarty, S., Manoj, A., Li, M., Ruben, A. J., Li, T., ... Seder, R. A. (2016). Protection against malaria at 1 year and immune correlates following PfSPZ vaccination. Nature medicine, 22(6), 614–623. https://doi.org/10.1038/nm.4110
6. Olotu, A., Fegan, G., Wambua, J., Nyangweso, G., Leach, A., Lievens, M., Kaslow, D. C., Njuguna, P., Marsh, K., & Bejon, P. (2016). Seven-Year Efficacy of RTS,S/AS01 Malaria Vaccine among Young African Children. The New England journal of medicine, 374(26), 2519–2529. https://doi.org/10.1056/NEJMoa1515257

7. Olotu, A., Urbano, V., Hamad, A., Eka, M., Chemba, M., Nyakarungu, E., Raso, J., Eburi, E., Mandumbi, D. O., Hergott, D., Maas, C. D., Ayekaba, M. O., Milang, D. N., Rivas, M. R., Schindler, T., Embon, O. M., Ruben, A. J., Saverino, E., Abebe, Y., Kc, N., ... Hoffman, S. L. (2018). Advancing Global Health through Development and Clinical Trials Partnerships: A Randomized, Placebo-Controlled, Double-Blind Assessment of Safety, Tolerability, and Immunogenicity of PfSPZ Vaccine for Malaria in Healthy Equatoguinean Men. The American journal of tropical medicine and hygiene, 98(1), 308–318. https://doi.org/10.4269/ajtmh.17-0449
8. RTS,S Clinical Trials Partnership (2015). Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet (London, England), 386(9988), 31–45. https://doi.org/10.1016/S0140-6736(15)60721-8
9. Seder, R. A., Chang, L. J., Enama, M. E., Zephir, K. L., Sarwar, U. N., Gordon, I. J., Holman, L. A., James, E. R., Billingsley, P. F., Gunasekera, A., Richman, A., Chakravarty, S., Manoj, A., Velmurugan, S., Li, M., Ruben, A. J., Li, T., Eappen, A. G., Stafford, R. E., Plummer, S. H., ... VRC 312 Study Team (2013). Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine. Science (New York, N.Y.), 341(6152), 1359–1365. https://doi.org/10.1126/science.1241800
10. World Health Organization. (2016). WHO Position paper: Malaria vaccine. Weekly Epidemiological Record No4, 91, 33-52.
11. World Health Organization. (2018). World Malaria Report 2018. Available at https://www.who.int/malaria/publications/country-profiles/profile_mys_en.pdf?ua=1

ZIKA

Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus that was first identified in Uganda in 1947 in monkeys. Outbreaks of ZIKV disease have been recorded in Africa, the Americas, Asia and the Pacific. Outbreak of ZIKV disease was reported from the Island of Yap (Federated States of Micronesia) in 2007, followed by a large outbreak of ZIKV infection in French Polynesia in 2013 and other countries and territories in the Pacific.

In March 2015, Brazil reported a large outbreak of rash illness, soon identified as ZIKV infection, and in July 2015, found to be associated with Guillain-Barré syndrome. In October 2015, Brazil reported an association between ZIKV infection and microcephaly. Outbreaks and evidence of transmission soon appeared throughout the Americas, Africa, and other regions of the world. To date, more than 80 countries and territories have reported evidence of mosquito-transmitted ZIKV infection.

In Malaysia, the ZIKV has been isolated in *Aedes aegypti* mosquitoes in 1960s. The first ZIKV case in Malaysia was officially reported in September 2016; a Malaysian woman with fever and facial rash a week after returning from a visit to Singapore, tested positive for ZIKV. The first local infection was detected in a 61-year-old man from Kota Kinabalu. In Malaysia, ZIKV infection was not widespread compared to outbreaks in countries nearby such as Singapore and Thailand, and to date the number of laboratory-confirmed cases is eight.

The risk of congenital malformations following infection in pregnancy remains unknown. An estimated 5–15% of infants born to women infected with ZIKV during pregnancy have evidence of ZIKV-related complications. Congenital malformations occur following both symptomatic and asymptomatic infection.

Upcoming Vaccines

There is no treatment available for ZIKV infection or its associated diseases. The public health value proposition for a Zika vaccine is to prevent prenatal ZIKV infection and congenital ZIKV syndrome, resulting in microcephaly, other nervous system malformations and pregnancy-related complications.

Therefore, the immunisation of women of reproductive age, including pregnant women, is considered to be of highest priority. In addition to vulnerability during the first trimester, evidence is accumulating that ZIKV infection in the 2nd and 3rd trimesters can also lead to adverse fetal and post-natal outcomes.

Vaccines

Currently no vaccine is registered. Various vaccine candidates have been developed and are in various stages of preclinical and clinical development. Clinical trials involving candidate DNA and purified inactivated virus vaccines showed all were safe and well-tolerated in the small number of volunteers and all induced neutralising antibodies, although these varied by vaccine candidate and dosing regimen

i. DNA vaccine developed by NIAID's Vaccine Research Center (VRC) has been approved for Phase 2 clinical trials in humans. The strategy is similar to the investigational flavivirus vaccine for West Nile virus infection. The vaccine consists of a DNA plasmid encoding the E and PrM proteins which make up the outer protein coat of the Zika virion. Results of Phase 1 trials indicate the optimised vaccine is safe and able to induce a neutralising antibody response against ZIKV virus.

   A Phase 2 clinical trial (VRC 705) was launched in 2017, which enrolled healthy adult and adolescent participants in areas of confirmed or potential active mosquito-transmitted ZIKV infection. The trial further evaluates the safety and immunogenicity of the vaccine and will assess the optimal dose for administration. It will also attempt to determine if the vaccine can effectively prevent disease caused by ZIKV infection.

ii. A modified mRNA vaccine developed in collaboration with Moderna Therapeutics containing the E and PrM proteins is undergoing concurrent phase 1 and 2 clinical trials.

iii. A live attenuated vaccine, rZIKV/D4Δ30-713 is undergoing phase 1 clinical trials. This vaccine is based on the dengue vaccine Dengvaxia (NIH, NIAID, US). The chimeric virus consists of a dengue virus type 4 backbone that expresses ZIKV surface proteins.

iv. A purified inactivated vaccine (ZPIV) is currently under development by the Walter Reed Army Institute of Research (WRAIR). This vaccine is based on the same technology used to develop a vaccine against Japanese Encephalitis Virus.

v. Multiple vaccines are also being developed using safe, non-pathogenic, viruses as vectors for immunogenic ZIKV proteins. One phase 1 trial is using the Measles virus as a vector and was completed in April 2018. Another vaccine platform makes use of Adenovirus as a vector and phase 1 studies will be complete in 2019.

References

1. Abbink, P., Stephenson, K.E., Barouch, D.H. (2018). Zika virus vaccines. Nature Reviews Microbiology. 16 (10): 594–600. doi:10.1038/s41579-018-0039-7. Available at https://www.who.int/immunization/research/development/WHO_UNICEF_Zikavac_TPP_Feb2017.pdf?ua=1
2. Barrett A.D.T. (2018). Current status of Zika vaccine development: Zika vaccines advance into clinical evaluation. NPJ Vaccines; 3: 24. doi: 10.1038/ s41541-018-0061-9.
3. Centers for Disease Control and Prevention, US. Zika Travel Information available at https://wwwnc.cdc.gov/travel/page/zika-travelinformation
4. Fernandez, E., & Diamond, M. S. (2017). Vaccination strategies against Zika virus. Current opinion in virology, 23, 59–67. https://doi.org/10.1016/j.coviro.2017.03.006
5. National Institute of Allergy and Infectious Diseases. Zika Virus Vaccines. Available at https://www.niaid.nih.gov/diseases-conditions/zika-vaccines. Accessed December 2019.
6. WHO/UNICEF Zika Virus (ZIKV) Vaccine Target Product Profile (TPP): Vaccine to protect against congenital Zika syndrome for use during an emergency Updated February 2017.
7. Woon, Y. L., Lim, M. F., Tg Abd Rashid, T. R., Thayan, R., Chidambaram, S. K., Syed Abdul Rahim, S. S., Mudin, R. N., & Sivasampu, S. (2019). Zika virus infection in Malaysia: an epidemiological, clinical and virological analysis. BMC infectious diseases, 19(1), 152. https://doi.org/10.1186/s12879-019-3786-9

Adults Who Missed Childhood Immunisation

Table 21.1
Recommended Vaccines for Adults Who Missed Childhood Immunisation

All adults should complete a primary series of the following vaccines and toxoids as quickly as possible if they have not done so during childhood.

Adults: Age group	Vaccine Recommended	Schedule	Comments
All Adults	Tetanus Diphtheria Pertussis	Combined tetanus, diphtheria and pertussis (Tdap): 1st dose of Tdap followed by 2nd dose of Td given 4 weeks later & 3rd dose of Td 6–12 months after 2nd dose. Booster (Td): every 10 years	Doses need not be repeated when vaccine schedule was delayed. Persons with uncertain histories of receiving diphtheria, tetanus and pertussis vaccination should receive primary vaccination schedule and Boosters.
All Adults	Poliomyelitis	A single booster dose of parenteral Polio vaccine every 10 years	There are still pockets of polio outbreaks in certain countries including Indonesia and the Indian subcontinent

Adults: Age group	Vaccine Recommended	Schedule	Comments
Adults aged 18-64 years	Measles Mumps Rubella	2 doses of measles-mumps-rubella (MMR) live vaccine; given at least 1 month apart	Recommended if no history of physician-documented Infection or laboratory evidence of immunity
All Adults	Hepatitis B	3 doses; 1st dose of Hep B vaccination, followed by 2nd dose that is given 4 weeks after the first dose and the 3rd dose that is given 6 months after the 1st dose	

Elderly And Patients With Chronic Illnesses

Table 21.2
Immunisations for the Elderly

Vaccine recommended	Category	Schedule	Comments
Pneumococcal	All adults 60 years and above who are previously unvaccinated or of unknown vaccination status	See schedule on page 132	-
Influenza	All elderly ≥50 years	1 dose administered annually	-
Zoster	All elderly ≥60 years old regardless of report of prior zoster infection	For Zostavax vaccine 1 time single dose, no 2nd dose needed	Neither taking varicella history nor serologic testing for varicella immunity are needed before administration of zoster vaccine

Vaccine recommended	Category	Schedule	Comments
Tetanus, diphtheria and pertussis (Tdap)	Complete vaccine series is indicated for elderly patients with uncertain vaccine history or with fewer than 3 recorded doses.	Primary vaccination: 3 doses with 1st dose of Tdap and 2nd dose with tetanus and diphtheria toxoid (Td); at least 4 weeks apart; 3rd of Td dose 6-12 months later Booster with Td at 10 years interval.	Tdap should be administered regardless of interval since last tetanus or diphtheria toxoid-containing vaccine

Table 21.3
Immunisations for Patients with Chronic Diseases

Category	Vaccines Recommended	Schedule	Comments
Residents of nursing homes and other chronic care facilities	Influenza*	Annual vaccination	Vaccination can be given throughout the year. Use the most recent formulation
	Pneumococcal	See schedule on page 132	
Patients with chronic illnesses (eg chronic pulmonary, cardiac, renal and liver disease, diabetes mellitus)	Pneumococcal (see page 132) Influenza (see page 95) Hepatitis B (see page 67 for end-stage renal disease, haemodialysis)	Please refer to relevant sections	

* Influenza vaccination is strongly recommended for all adults 50 years and above.

Healthcare workers

On the basis of documented nosocomial transmission, HCWs are considered to be at significant risk for acquiring and transmitting the following vaccine preventable infections.

The following vaccinations (table 21.4) are strongly recommended for all HCWs:

Table 21.4
Immunisation for Healthcare Workers

Category of HCW	Vaccines Recommended	Timing	Comments
All HCW **Includes all workers and students directly involved in patient care or the handling of human tissues**	Hepatitis B	Primary vaccination should be given at onset of career for those without documented evidence of a complete HepB vaccine series or serologic evidence of immunity.	Prevaccination serologic screening and post-vaccination testing recommended.
	Measles, mumps and rubella (MMR)	Primary vaccination (2 doses with at least a month apart) before onset of career for HCWs who do not have documented vaccination, physician-diagnosed infection or serologic evidence of immunity	Booster doses not necessary. MMR vaccine preferred.

Special Groups

Category of HCW	Vaccines Recommended	Timing	Comments
All HCW **Includes all workers and students directly involved in patient care or the handling of human tissues**	Influenza	Annual vaccination	Use the most recent available formulation
	Pertussis (Tdap)	HCWs should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap	Tdap can be administered regardless of interval since the last tetanus or diphtheria-containing vaccine
	Varicella	HCWs who do not have a reliable history of varicella infection or serologic evidence of immunity should be given two doses 4-8 weeks apart.	Booster doses are not necessary

** The category of healthcare workers (HCWs) include persons who provide healthcare to patients or work in institutions that provide patient care e.g. doctors, nurses, emergency medical personnel, dental professionals and students, medical and nursing students, laboratory technicians, hospital volunteers and support staff providing patient care in healthcare institutions.*

The following vaccines are **not routinely recommended for HCWs (exceptions listed in parenthesis)**

- **BCG**
  (Only considered for HCWs in areas where multidrug resistant tuberculosis is prevalent, where there is strong likelihood of infection & when comprehensive infection control measures have failed to prevent transmission to HCWs.)

- **Hepatitis A**
  (Consider for HCW who work in remote Indigenous communities or with Indigenous children)

- **Typhoid**
  (Considered in workers in microbiology laboratories who frequently work with *Salmonella* Typhi.)

- **Meningococcal polysaccharide vaccine**
  (Indicated for laboratory personnel working frequently with *Neisseria meningitidis*)

- **Vaccinia**
  (Indicated only for laboratory workers involved with orthopox viruses and certain health-care workers involved in clinical trials of vaccinia recombinant vaccines)

- **Anthrax**
  (Indicated for laboratory personnel working with *Bacillus anthracis*)

- **Rabies**
  (Pre-exposure vaccination only indicated for laboratory workers directly involved with testing or isolating rabies virus)

Human Immunodeficiency Virus (HIV)

Table 21.5
Immunisation for HIV Patients

Vaccine	Cd4 count ≤ 200 cells/mm³	Cd4 count > 200 cells/mm³
Hepatitis A[1]	R	R
Hepatitis B[2]	R	R
Hib	UI	UI
HPV[3]	R	R
Influenza (inactivated)	R	R
MMR	C	UI
Meningococcus[4]	R	R
Pneumococcus (PCV13 and PPV23)[5]	R	R
Rabies	UI	UI
Tetanus-Diptheria (Td)	UI	UI
Varicella[6]	C	UI
Yellow Fever[7]	C	UI
Zoster[8]	C	UI

R – recommended; C – contraindicated; UI – Usual indication

1. Recommended for people who inject drugs (PWID), men who have sex with men (MSM), chronic hep B or C virus infections, haemophiliacs or those receiving clotting factor concentrates
2. For nonimmune (anti-HBs < 10mIU/ml): 20 mcg as 4 dose series at 0, 1, 2, and 6 months. Better immune response in those with HIV viral load suppressed.
3. Males and females through 26 years. 3 dose series at 0, 1-2, and 6 months
4. 2 doses of MenACWY given ≥2 months apart and booster given every 5 years

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5. Previously unvaccinated: 1 dose of PCV13 followed by 1 dose of PPV23 >8 weeks later (preferably when CD4 count >200 cells/mm^3). Repeat PPV23 dose 5 years later. Previously vaccinated with PPV23, give PCV13 at >1 year later followed by PPV-23, 5 years after the previous dose. PCV13 can be given at any Cd4 cell count. For PPV23 is it preferable to wait until CD4 count is> 200 cells/mm^3.
6. VZV seronegative and Cd4 count >200. 2 doses 3 months apart. Discontinue antiherpetic medications (e.g. acyclovir) at the time of vaccination and for the next 4 weeks
7. In those with CD4 count >200 cells/mm2, better immune response is shown in those with HIV viral load suppression*.
8. Shown to be immunogenic in those with Cd4 count > 200 and suppressed HIV viral load#. Discontinue antiherpetic medications (e.g. acyclovir) at the time of vaccination and for the next 4 weeks.

References

1. Benson, C. A., Andersen, J. W., Macatangay, B. J. C., Mailliard, R. B., Rinaldo, C. R., Read, S., Bozzolo, D. R., Purdue, L., Jennings, C., Keefer, M. C., Glesby, M., Tebas, P., Russell, A. F., Martin, J., Annunziato, P., Popmihajlov, Z., & Lennox, J. L. (2018). Safety and Immunogenicity of Zoster Vaccine Live in Human Immunodeficiency Virus-Infected Adults With CD4+ Cell Counts >200 Cells/mL Virologically Suppressed on Antiretroviral Therapy. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 67(11), 1712–1719. https://doi.org/10.1093/cid/ciy242247
2. Pacanowski, J., Lacombe, K., Campa, P., Dabrowska, M., Poveda, J.-D., Meynard, J.-L., Poirot, J.-L., Fonquernie, L., & Girard, P.-M. (2012). Plasma HIV-RNA is the key determinant of long-term antibody persistence after Yellow fever immunization in a cohort of 364 HIV-infected patients. Journal of Acquired Immune Deficiency Syndromes (1999), 59(4), 360–367. https://doi.org/10.1097/QAI.0b013e318249de59

Immunocompromised Patients

Table 21.6
Immunisation for Patients with Acute Leukemia, Lymphoma, Multiple Myeloma and Solid Tumors

Vaccine type	Recommendation	Vaccination schedule/ comments
Inactivated and conjugated vaccines		
Inactivated Influenza (IM)[a] Avoid live attenuated vaccine	RECOMMENDED in patients receiving treatment for acute leukemia, lymphoma, solid cancers should be vaccinated annually against influenza.	Inactivated form only. Annually (2-dose series given at least 2 weeks prior to chemotherapy). Patients receiving rituximab should receive the vaccine 6 months after therapy because of poor immune response.
Pneumococcal (IM or SC) ^^ • PCV 13 conjugate vaccine • PPV 23 polysaccharide vaccine	RECOMMENDED in adult patients receiving treatment for acute leukemia, myeloma, lymphoma, cGvHD. Acute Leukaemia patients should receive pneumococcal vaccination before treatment.	Vaccine should be given at 4-6 weeks (min 2 weeks) prior to chemotherapy. If pre-chemo vaccination is not possible, administer vaccine at least 3 months after completion of chemotherapy. PCV13-PPV23 sequence is preferred: 1. 1 dose of PCV13 vaccine 2. 1 dose of PPV23 vaccine at least 8 weeks after PCV13 vaccine 3. Booster doses of PPV23 vaccine at least 5 years after the last PPV23 vaccine, up to a maximum of 3 doses of PPV23 in a lifetime.

Vaccine type	Recommendation	Vaccination schedule/ comments
Diphtheria-Tetanus-Pertussis (IM)	RECOMMENDED in case of incomplete vaccination status or requirement of booster vaccination adults with acute leukemia, lymphoma, solid cancers after chemotherapy.	No additional dose needed if up to date with vaccination. Tdap: reduced dose of diphtheria is recommended for adult patients. It is also recommended that a single dose of Tdap replace one of the routine Td boosters. Td every 10 years.
Haemophilus influenzae type b (Hib) (IM)[$]	OPTIONAL. May be considered in unvaccinated patients.	None needed, unless post-treatment titers are undetectable. If the titer is low, revaccination at least 2 weeks prior to chemotherapy to ensure maximal response or at least 3 months after completion of chemotherapy
Hepatitis A (IM)	OPTIONAL	Only recommended if traveling to endemic areas or as post exposure prophylaxis
Hepatitis B (IM)*** high dose formulation	RECOMMENDED in: seronegative or incomplete vaccination status for adults with acute leukemia, lymphoma and solid cancers.	Hep B 3-dose series within 6–12 months after remission after bone marrow recovery (not while on immunosuppressive therapy). Another option is to combine passive and active prophylaxis with both vaccine and hyperimmunoglobulin. Also, Hepatitis A&B co-immunisation is feasible. Assess titre after chemotherapy.

Vaccine type	Recommendation	Vaccination schedule/ comments
IPV (IM or SC)	OPTIONAL	Not routinely needed unless post-treatment titres are undetectable
Meningococcal vaccine • MCV4 (IM): for age 2-55 years • MPSV4 (SC): 56 years and older	RECOMMENDED Vaccination against meningococcus is routinely recommended for patients with (functional) asplenia.	MCV4 (1 week prior to starting therapy); repeat 5 years after completion of therapy.
Human papillovirus (HPV) quadrivalent vaccine (IM)	OPTIONAL Age specific (9-26 yr old) for the prevention of cervical cancer, anal cancer, and genital warts. 3-dose series	If vaccination against HPV is indicated, vaccination should be performed regardless of immunosuppression; however, immune-response might be reduced.
Live vaccines		
MMR (SC)§	CONTRAINDICATED during chemotherapy. Consider vaccination in seronegative (not previously exposed or vaccinated).	None needed if childhood vaccination up to date. If previously vaccinated, check post-treatment titre If low titre, administer at least 3 months after completion of chemotherapy (particular in leukemic in remission).
VZV (SC)#	CONTRAINDICATED during chemotherapy. Consider vaccination in seronegative (not previously exposed or vaccinated).	Immunisation against VZV >24 months after completion of therapy may thus be considered for patients with acute leukemia. 2-dose series (at least 4-8 week apart)

cGvHD ; chronic graft versus host disease

Footnote:

The risk of severe infection is influenced by the underlying malignancy and the cancer specific therapies.

Immune response to the vaccine is reduced during chemotherapy therefore, vaccination should be avoided during treatment. Patients given inactivated vaccines >14 days before antineoplastic treatment do not require revaccination, unless vaccination status is incomplete or refresher vaccination is indicated. Patients vaccinated during chemotherapy should be revaccinated ≥ 3 months after completion of chemotherapy and ≥ 6 months after anti-B cell antibodies

Live vaccines, e.g. against MMR, yellow fever and varicella, are generally contraindicated during chemotherapy [including maintenance therapy with monoclonal antibodies or immunomodulatory agents, e.g. lenalidomide, as well as conditions with significant immunosuppression]. After completion of immunosuppressive therapy, live vaccines against MMR and varicella might be considered after assessment of antibody titres.

[a] – Administer inactivated influenza vaccine (IIV) annually to patients with hematological malignancies (strong, moderate) or solid tumor malignancies (strong, low) except those receiving anti-B-cell antibodies such as rituximab or alemtuzumab (weak, low). The Infectious Diseases Society of America also suggests that IIV be avoided in patients receiving intensive chemotherapy such as for induction or consolidation therapy for acute leukemia (weak, low). However, we favor giving an inactivated influenza vaccine to such patients given the need for annual administration to protect against circulating seasonal strains of influenza. Administration of inactivated vaccines other than IIV, which are routinely recommended for healthy children in the annually updated United States Centers for Disease Control and Prevention (CDC) recommendations, can be considered for children with malignancies who are receiving maintenance chemotherapy (weak, low). However, vaccines administered while receiving cancer chemotherapy should not be considered valid doses (strong, low). Administration of indicated inactivated vaccines 2 or more weeks prior to chemotherapy is preferred. IIV can be administered ≤ 3 months after chemotherapy, but response rate may be low. Two doses of influenza vaccine may be more immunogenic than one and are well tolerated in children and young adults. VACANCE trial suggest a second administration of influenza vaccine in cancer patients as this increased seroconversion from 44% to 73%. It is also recommended that family members and caretakers also receive annual inactivated influenza vaccination if there is contact with those who are immunosuppressed. The observed side effects of the inactivated influenza vaccine are similar in all populations in that they are generally mild and may include soreness or pain around the injection site, fever, fatigue, or myalgia.

^^ If pretreatment vaccination is not feasible, we recommend vaccination after the first chemotherapy cycle and repetition 3 months after chemotherapy, PCV13 is more immunogenic than PPV23. Due to a lower immunogenic response, patients receiving treatment for multiple myeloma, Hodgkin and non-Hodgkin lymphomas, and cGVHD, as well as those who have undergone total-body irradiation, should be vaccinated with PCV13 instead of PPV23. For patients aged ≥ 19 years who have received PPV23, PCV13 should be administered after an internal of ≥ 1 years after the last PPV23 dose (weak, low).

[$] Adult patients with malignancies are at increased risk for HiB infections, particularly HiB-induced pneumonia.

***HBV vaccine should not be given while patients are on immunosuppressive therapy. As immune-response for HBV-vaccine was shown to be impaired in this population [23], patients with AL should receive several doses (AIII) vaccination against HBV is recommended in lymphoma, myeloma patients in case of incomplete vaccination status or if a vaccination refreshing is required (BII). Inadequate immune-response should always be considered and in individual patients, passive immunisation against HBV could offer short-term protection.

Assessing titres of diphtheria, tetanus and HBV might be useful after chemotherapy.

These live viral vaccines should not be administered during chemotherapy unless indicated based on CDC recommendations AND the patient is not immunosuppressed AND there will be an interval of ≥ 4 weeks prior to initiation of chemotherapy. Adult cancer patients seronegative for VZV show increased rates of complications (e.g. dissemination, mortality), if primarily infected. Only one study investigated immunity and safety of VZV vaccine in (pediatric) leukemia patients and showed benefits regarding immunity against chickenpox for at least 3 years.

§ Although MMR vaccine has been given safely three months after completion of chemotherapy, data on the safety, immunogenicity, and efficacy of varicella or zoster vaccine after completion of chemotherapy are not available.

References

1. Arrowood, J. R., & Hayney, M. S. (2002). Immunization recommendations for adults with cancer. Annals of Pharmacotherapy, 36(7-8), 1219-1229.
2. Ljungman, P. (2012). Vaccination of immunocompromised patients. Clinical Microbiology and Infection, 18, 93-99.
3. Practices, A. C. o. I. (2012). Recommended adult immunization schedule: United States, 2012. Annals of internal medicine, 156(3), 211.
4. Rieger, C., Liss, B., Mellinghoff, S., Buchheidt, D., Cornely, O., Egerer, G., Heinz, W., Hentrich, M., Maschmeyer, G., & Mayer, K. (2018). Anti-infective vaccination strategies in patients with hematologic malignancies or solid tumors—Guideline of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Annals of Oncology, 29(6), 1354-1365.
5. Sandherr, M., Hentrich, M., von Lilienfeld-Toal, M., Massenkeil, G., Neumann, S., Penack, O., Biehl, L., & Cornely, O. A. (2015). Antiviral prophylaxis in patients with solid tumours and haematological malignancies—update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Annals of Hematology, 94(9), 1441-1450.
6. Tsang, V. (2012). Vaccination Recommendations for the Hematology and Oncology and Post–Stem Cell Transplant Populations. Journal of the Advanced Practitioner in Oncology, 3(2), 71.

Relationship between Monoclonal Antibodies, Kinase Inhibitors and Immune Checkpoint Blockade and Vaccination

Monoclonal antibodies against CD20 result in near complete B cell depletion for up to 6 months after therapy. Although the majority of patients show complete recovery of B cells 1 year after therapy, prolonged B cell depletion and hypogammaglobulinemia may occur, making vaccination strategies challenging.

As a functioning B cell compartment is required for an adequate immune response, vaccination within the first 6 months after anti-CD20 therapy is generally discouraged.

Within the first year after anti-CD20 therapy, assessment of antibody titers and revaccination if indicated might be an effective strategy to achieve protective antibody levels despite a diminished immune response. Particularly in case of seasonal influenza vaccine after anti-CD20 therapy, administration of a second booster vaccine has been shown to significantly increase humoral immune response.

While most data on vaccination strategies have been obtained with the oldest anti-CD20 antibody rituximab, it is generally accepted that these recommendations be transferable to other anti-CD20 antibodies such as ofatumumab or obinutuzumab as well as to other temporarily B cell depleting therapies such as the anti-CD3xCD19 bispecific T-cell engager blinatumomab.

Due to the different pathways affected, the effect of kinase inhibitors on immune response to vaccination is entirely dependent on the drug in question. In a small study of patients with metastatic renal cell carcinoma treated with the tyrosine kinase inhibitors sorafenib or sunitinib, no significant difference regarding protective antibody responses after influenza vaccination could be observed compared with healthy controls. Another small study with chronic lymphocytic leukemia patients treated with ibrutinib showed seroprotective titers against common influenza virus strains after vaccination in up to 74% of patients. Therefore, decisions on vaccination need to be made on a case-by-case basis. In patients receiving kinase inhibitors, assessment of antibody titers and revaccination (if necessary) is recommended for adequate seroprotection.

Due to their novelty, data on vaccination strategies in patients treated by immune checkpoint inhibitors, such as anti-PD1, anti-PD-L1 or anti-CTLA4 antibodies, are limited. However, considering their mechanism of action, immune checkpoint inhibitors are likely to enhance rather than diminish immune response and have even been safely explored as vaccine adjuvants. As patients receiving immune checkpoint inhibitors are still at increased risk of infections due to their underlying malignancy, they should receive all appropriate vaccines at the earliest convenience to avoid infectious complications or delay in therapy.

References

1. Cabanillas, F., Liboy, I., Pavia, O., & Rivera, E. (2006). High incidence of non-neutropenic infections induced by rituximab plus fludarabine and associated with hypogammaglobulinemia: a frequently unrecognized and easily treatable complication. Annals of Oncology, 17(9), 1424-1427.
2. Chiou, W.-Y., Hung, S.-K., Lai, C.-L., Lin, H.-Y., Su, Y.-C., Chen, Y.-C., Shen, B.-J., Chen, L.-C., Tsai, S.-J., & Lee, M.-S. (2015). Effect of 23-valent pneumococcal polysaccharide vaccine inoculated during anti-cancer treatment period in elderly lung cancer patients on community-acquired pneumonia hospitalization: a nationwide population-based cohort study. Medicine, 94(26).
3. de Lavallade, H., Garland, P., Sekine, T., Hoschler, K., Marin, D., Stringaris, K., Loucaides, E., Howe, K., Szydlo, R., & Kanfer, E. (2011). Repeated vaccination is required to optimize seroprotection against H1N1 in the immunocompromised host. Haematologica, 96(2), 307-314.
4. Madan, R. A., Mohebtash, M., Arlen, P. M., Vergati, M., Rauckhorst, M., Steinberg, S. M., Tsang, K. Y., Poole, D. J., Parnes, H. L., & Wright, J. J. (2012). Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. The lancet oncology, 13(5), 501-508.
5. McLaughlin, P., Grillo-López, A. J., Link, B. K., Levy, R., Czuczman, M. S., Williams, M. E., Heyman, M. R., Bence-Bruckler, I., White, C. A., & Cabanillas, F. (1998). Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. Journal of clinical oncology, 16(8), 2825-2833.
6. Mulder, S. F., Jacobs, J. F., Nordkamp, M. A. O., Galama, J. M., Desar, I. M., Torensma, R., Teerenstra, S., Mulders, P. F., Vissers, K. C., & Punt, C. J. (2011). Cancer patients treated with sunitinib or sorafenib have sufficient antibody and cellular immune responses to warrant influenza vaccination. Clinical Cancer Research, 17(13), 4541-4549.
7. Rieger, C., Liss, B., Mellinghoff, S., Buchheidt, D., Cornely, O., Egerer, G., Heinz, W., Hentrich, M., Maschmeyer, G., & Mayer, K. (2018). Anti-infective vaccination strategies in patients with hematologic malignancies or solid tumors—Guideline of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Annals of Oncology, 29(6), 1354-1365.
8. Sun, C., Gao, J., Couzens, L., Tian, X., Farooqui, M. Z., Eichelberger, M. C., & Wiestner, A. (2016). Seasonal influenza vaccination in patients with chronic lymphocytic leukemia treated with ibrutinib. JAMA oncology, 2(12), 1656-1657.

Table 21.7
Immunisation For Blood And Marrow Transplant Recipients (Allogeneic And Autologous)

Vaccine		Time after HSCT				
	No. of doses[a]	**Visit 1**	**Visit 2**	**Visit 3**	**Booster 12 months after first vaccination**	**Comments**
Inactivated vaccine or toxoid						
Diphtheria, Tetanus, Pertussis	3[b]	DTaP	DTaP	DTaP	DTaP	From 6 to 12 months after transplant: three doses of DTaP at 1-2 month intervals are recommended, followed by a booster 18 months after HSCT. Full dose (D) and full dose acellular vaccine (aP) are preferred. It is recommended that post-transplant patients receive DTaP due to its higher response rate as compared to Tdap.
Polio (Inactivated vaccine only)	3[b]	IPV	IPV	IPV	IPV	From 6 to 12 months: three doses at 1–2-month intervals are recommended; booster doses should be administered. Inactivated vaccine only

Vaccine		Time after HSCT				
	No. of doses[a]	Visit 1	Visit 2	Visit 3	Booster 12 months after first vaccination	Comments
Inactivated vaccine or toxoid						
Hib. (Conjugate vaccine preferred)	3	Hib	Hib	Hib	Hib	From 6 to 12 months: three doses at 1-month intervals are recommended. Alternatively, to decrease the overall number of vaccine doses, administer three doses of a combined diphtheria-tetanus-pertussis-Hib vaccine.
Hep B		Hep B	Hep B	Hep B	Booster[c]	Before transplant, patients who are negative for all HBV markers that are transplanted with a graft from an anti-HBc positive donor should be vaccinated if possible and receive anti-HBV immunoglobulins. From 6 to 12 months after HSCT for: (i) seronegative patients before HSCT with a donor with positive anti-HBc, (ii) previously infected and anti-HBS < 10 mIU/ml.

Vaccine		Time after HSCT				
	No. of doses[a]	Visit 1	Visit 2	Visit 3	Booster 12 months after first vaccination	Comments
Inactivated vaccine or toxoid						
Pneumococcal	3 x PCV13, 1 x PPV23	PCV13	PCV13	PCV13	PPV23 booster	From 6 months after HSCT three doses PCV13 at 1-monthly interval are recommended. The PCV13 is more immunogenic and preferred but the spectrum of protection is narrower. HSCT recipients obtain better response to PCV13 than PPV23. PPV23 may be given at 18 months to broaden the coverage if patient has no cGVHD that requires immunosuppression. Adjunctive antibiotic prophylaxis may be given for patients with cGVHD.
Influenza	1	Influe-nza	Influe-nza		Booster annually	Administer first dose vaccine 6 months after transplant. The second dose 4 weeks after 1st dose. Booster annually

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Vaccine		Time after HSCT				
	No. of doses[a]	Visit 1	Visit 2	Visit 3	Booster 12 months after first vaccination	Comments
Inactivated vaccine or toxoid						
HPV	3	HPV	HPV (2 month after first dose)	HPV (6 month after first dose)		Administer first dose from 6 to 12 months after transplant based on guidelines for the general population. It is recommended for healthy adolescents or young adults in most countries to prevent human papillomavirus-related malignancies.
Meningo-coccal (Conjugate vaccine preferred)	2				Booster dose has not been established	Only for patient at risk including those with asplenia, who travel to high risk areas (Hajj). From 6 months after transplantation at least two doses of either a monovalent or tetravalent C vaccine and meningococcal B vaccine.

Vaccine		Time after HSCT				
	No. of doses[a]	Visit 1	Visit 2	Visit 3	Booster 12 months after first vaccination	Comments
Live-Attenuated virus						
MMR	1-2	Not recommended				Contraindicated immediately post transplantation. Consider after 24 months post transplantation in a seronegative patient who is off all immuno- suppressive therapy and no evidence of chronic GVHD, no relapse of underlying disease.
Varicella	1-2	Not recommended				Not indicated in seropositive patients for the prevention of herpes zoster (DIII) to all varicella, susceptible healthcare workers or family members in close contact with patient.
Zoster		Not recommended				
BCG		Not recommended				

Footnote:

[a] if not specified, otherwise, the interval between dose is 1 month,

[b] the interval between dose is 1-2 month,

[c] Check titres 4-8 weeks after last dose of post-transplant vaccine; if anti-HBs is < 10 mIU/ml, an additional 3 doses should be considered, but the benefit of this second series of vaccination is uncertain. A high dose formulation is preferred for these booster doses.

cGvHD; chronic graft versus host disease.

NOTES

1. Vaccination schedules are similar for allogeneic and autologous HCT recipients, but grading of recommendation changes for some vaccines.
2. Live attenuated vaccines (MMR, varicella) should not be given within the first 2 years after HSCT during active Graft versus host disease (GvHD) (DIII). Limited data regarding safety and efficacy.
3. Inactivated vaccine can be given if the patient has chronic GVHD.
4. Inactivated Polio form (IPV) and oral Polio vaccine (OPV) are not interchangeable.
5. In patients receiving prednisone ≥ 0.5 mg/kg bodyweight per day as part of a combination therapy or a three-agent immunosuppressive treatment is given, vaccination may be postponed until immunosuppression is reduced to a double combination or prednisone < 0.5 mg/ kg bodyweight daily in order to achieve a better vaccine response (BIII).
6. Following a complete revaccination program, regular assessment of seroprotection against diphtheria, poliomyelitis, tetanus, measles and HBV every 4-5 years is recommended in patients after HSCT (BIII).
7. Pneumococcal vaccine: There are 2 types of pneumococcal vaccine – conjugate vaccine (PCV13) and polysaccharide vaccine (PPV23). PCV13 is used for the primary series because the immunological response to conjugate vaccines is generally more immunogenic than polysaccharide vaccines but, the spectrum of protection is narrower and therefore the subsequent dose of PPV23 is given to broaden the immune response. The PPV23 covers 23 strains but is less immunogenic and may elicit inadequate response. It may be beneficial to use PPV23 as the fourth dose to broaden the immune response.
8. For transplant patients who wish to travel abroad, immunisation may be necessary. Patients should seek advice from their respective transplantation teams. Vaccines that should be safe for blood and marrow transplant patients intending to travel include:
    - Typhoid – The oral form is contraindicated,
    - Cholera – Not recommended because of low protective efficacy,
    - Hepatitis A – Both active and passive are safe.
    - The following vaccines are contraindicated: Yellow fever, Japanese encephalitis, oral polio vaccines
9. HBV

    Before allogeneic HSCT, patients who are negative for all HBV markers that are transplanted with a graft from an anti-HBc positive donor should be vaccinated if possible (B III) and could additionally receive anti-HBV immunoglobulins;

10. 6 months after allogeneic and autologous HSCT, patients who were negative for HBV before transplantation and patients who were vaccinated before transplant but lost their immunity at 6 months should be vaccinated (6–12 months after transplantation 3 doses should be administered 0, 1, and 6 months apart), (B II t); patients infected with HBV before HSCT (HBsAg negative and anti-HBc positive) should be assessed regularly for anti-HBs antibody titres and should be vaccinated if they have unprotective titres (< 10 IU/ml) (B III); if anti-HBs titres are 10ml/ml 1-2months after the initial series of 3 vaccine doses, a second series of 3 doses should be considered (CIII). In persons that are primary non-responders, a repeat vaccine series using high-dose vaccine can be administered. If seroconversion is not achieved, counselling regarding post-exposure prophylaxis and avoidance of high-risk behavior can be provided.
11. Donor vaccination may improve the immunity of patient's post-transplant especially in the case of tetanus, pneumococcus and Hib. However, no recommendations can be made in view of the practical difficulties and ethical issues.

References

1. Cordonnier, C., Einarsdottir, S., Cesaro, S., Di Blasi, R., Mikulska, M., Rieger, C., de Lavallade, H., Gallo, G., Lehrnbecher, T., & Engelhard, D. (2019). Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7). The Lancet Infectious Diseases, 19(6), e200-e212.
2. de la Cámara, R. (2019). Vaccinations. In E. Carreras, C. Dufour, M. Mohty, & N. Kröger (Eds.), The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies (pp. 207-219). Springer International Publishing. https://doi.org/10.1007/978-3-030-02278-5_29
3. Ljungman, P., Cordonnier, C., Einsele, H., Englund, J., Machado, C., Storek, J., & Small, T. (2009). Vaccination of hematopoietic cell transplant recipients. Bone marrow transplantation, 44(8), 521-526.
4. Rieger, C., Liss, B., Mellinghoff, S., Buchheidt, D., Cornely, O., Egerer, G., Heinz, W., Hentrich, M., Maschmeyer, G., & Mayer, K. (2018). Anti-infective vaccination strategies in patients with hematologic malignancies or solid tumors—Guideline of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Annals of Oncology, 29(6), 1354-1365.
5. Rubin, L. G., Levin, M. J., Ljungman, P., Davies, E. G., Avery, R., Tomblyn, M., Bousvaros, A., Dhanireddy, S., Sung, L., & Keyserling, H. (2014). 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clinical infectious diseases, 58(3), e44-e100.
6. Ullmann, A. J., Schmidt-Hieber, M., Bertz, H., Heinz, W. J., Kiehl, M., Krüger, W., Mousset, S., Neuburger, S., Neumann, S., & Penack, O. (2016). Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. Annals of Hematology, 95(9), 1435-1455.

Table 21.8
Immunisation For Solid Organ Transplant Adult Recipients

Timing Catch-up schedule (if needed)						
Vaccine	**Vaccination schedule**	**Visit 0**	**Visit 2 (1-2 months)**	**Visit 3 (6 months)**	**Booster dose**	**Comments**
DT or DTaP	1 dose	DT			Booster every 10 years	For those with no previous vaccination history, to give first dose as DTaP
Hib conjugate	1 dose					Consider for lung transplant recipients and children <18 years
Hepatitis B	3 doses at 0,1,6 months (pre-transplant is preferred)	Hep B	Hep B	Hep B	Booster if titre <10 ml IU/mL	Use high dose formulation Up to 4 doses may be used for immuno-compromised patients; check anti-HBs after complete vaccination
Hepatitis A	2 doses at 6-12 months apart	Hep A		Hep A		For patient at-risk only, include those for liver transplant, chronic liver disease or at-risk of HAV exposure (travel to endemic areas for HAV)

HPV	3 doses at 0, 1, 6 months					For patients who have not been vaccinated previously or did not complete the vaccine: Females aged 9-45 years, males 9-26 years and MSM >26 years, can be given before or after transplant
Influenza (inactivated)						IIV Recommended annually; high dose vaccines not routinely recommended. LAIV is contraindicated in immunocompromised patients
Polio (IPV)	1 dose (intramuscular IPV)	IPV				Recommended for patients at-risk only i.e. in endemic areas for occupational risk. Oral polio vaccine (OPV) is contraindicated in transplant recipients and their household contacts

Timing Catch-up schedule (if needed)						
Vaccine	**Vaccination schedule**	**Visit 0**	**Visit 2 (1-2 months)**	**Visit 3 (6 months)**	**Booster dose**	**Comments**
Meningococcal (MCV)	2 doses, 2 months apart	Meningococcal	Meningococcal		Booster dose 5 years later	For patient at-risk only, include those with asplenia, who travel to high risk areas (Hajj), received eculizumab post-transplant The conjugated vaccines (MCV) is preferred over polysaccharide vaccine (MPV)
Pneumococcal	2 doses, 8 weeks apart	PCV 13	PPV23		Booster dose 5 years later	PCV13-PPV23 sequence is preferred: 1. 1 dose of PCV13 vaccine 2. 1 dose of PPV23 vaccine at least 8 weeks after PCV13 vaccine

						3. Booster doses of PPV23 vaccine at least 5 years after the last PPV23 vaccine, up to a maximum of 3 doses of PPV23 in a lifetime.
Live Vaccines						
MMR	1-2 doses for pre-transplant only	MMR			A booster dose if no seroconversion	Not recommended after transplant
Varicella	2 doses for pre-transplant and at-risk only	Varicella	Varicella			Not recommended after transplant For those who are seronegative only

Footnote:
IIV, inactivated Influenza vaccine; LAIV, Live attenuated Influenza (inactivated); IPV, Inactivated Polio Vaccine; HPV, human papilloma virus; MMR, Measles-Mumps-Rubella, MSM, men who have sex with men

HBV: High-dose vaccine should be used pre-transplant in dialysis patients and after SOT.5 In general, anti-HBs titers should be monitored post-transplant and booster doses (1–3 boosters) should be administered if titers fall below protective levels (<10 IU/mL). In persons that are primary non-responders, a repeat vaccine series using high-dose vaccine can be administered. If seroconversion is not achieved, counselling regarding post-exposure prophylaxis and avoidance of high-risk behavior can be provided.

References

1. Danziger-Isakov, L., Kumar, D., & Practice, A. I. D. C. o. (2013). Vaccination in solid organ transplantation. American Journal of Transplantation, 13(s4), 311-317.
2. Rubin, L. G., Levin, M. J., Ljungman, P., Davies, E. G., Avery, R., Tomblyn, M., Bousvaros, A., Dhanireddy, S., Sung, L., & Keyserling, H. (2014). 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clinical infectious diseases, 58(3), e44-e100.
3. Stucchi, R. S., Lopes, M. H., Kumar, D., & Manuel, O. (2018). Vaccine recommendations for solid-organ transplant recipients and donors. Transplantation, 102(2S), S72-S80.

Miscellaneous Groups

Table 21.9

Category	Recommended Vaccines
Prisoners	Hep B
Men who have sex with men (MSM)	Hep B, Quadrivalent HPV
Injecting drug users (IDU)	Hep A, Hep B
People who work with children	Influenza (annual vaccination) Tdap MMR (if non-immune) Varicella (if non-immune)
Care-givers • carers for persons with developmental disabilities • staff of nursing homes and long term care facilities for persons of any age	Hep A Hep B Influenza (annual vaccination) Tdap MMR (if non-immune) Varicella (if non-immune)
Emergency and essential service workers • police/emergency workers/ armed • forces personnel/staff of correctional • facilities, prison or detention centres	Hep B Influenza (annual vaccination) Td or Tdap MMR (if non-immune) Varicella (if non-immune)

Travelers

Vaccination for travelers will depend on:

1. Country of visit
2. Duration and place of stay
3. Intended activities

The following websites provide updated information on immunisation for travelers and should be referred to when offering advice on travel vaccination.

- WHO International travel and health (www.who.int/ith)
- Centers for Disease Control (wwwnc.cdc.gov/travel/)
- International Association for Medical Assistance to Travelers (www.iamat.org)

Preferably travellers are advised to use the IHR 2005 International Certificate of Vaccination or Prophylaxis. The certificate is available from the WHO website at https://www.who.int/ihr/IVC200_06_26.pdf

Table 21.10
Vaccination Summary for Travelers

Category	Vaccine	Comments
Mandatory vaccination	Yellow fever for all travelers travelling to or from yellow fever endemic countries (See page 166) See page 270 for advice on Hajj and Umrah pilgrimage	These vaccines are legal requirements for travel. Failure to obtain vaccines could result in non-entry/ quarantine in destination as well as home country. Countries requiring yellow fever vaccination for entry do so in accordance with the International Health Regulations. Country requirements are subject to changes at any time.
Routine vaccination	Poliomyelitis (see page 139) Diphtheria/tetanus/pertussis (see page 36) Hepatitis B (see page 67) Measles/mumps/rubella (see page 107)	Although not mandatory all travelers are generally advised to ensure that they have these necessary vaccination and boosters. Administration of polio vaccine may be mandatory in some area in the countries (e.g. in Afghanistan and Pakistan) to all outgoing international travelers and incoming long-term visitors (i.e. > 4 weeks) of all ages, and an International Certificate of Vaccination as proof of vaccination. With the re-emergence of poliomyelitis in Sabah,

Category	Vaccine	Comments
		Malaysians who wish to travel overseas to polio-free countries will need to check with the respective embassies if they require an additional single dose of IPV/OPV 4 weeks to 12 months prior to international travel.
Selective use for travelers	Cholera (see page 31) Influenza (see page 95) Hepatitis A (see page 62) Japanese encephalitis (see page 101) Meningococcal (see page 125) Pneumococcal (see page 130) Rabies (see page 143) Typhoid (see page 155)	Recommendations for these vaccines depend on the countries of destination, the current outbreak situation at the time of travel, the purpose for travel, the time to time, it is prudent to access the latest advisories from the following sites: wwwnc.cdc.gov/travel/ www.who.int/ith www.iamat.org

Vaccination for Hajj and Umrah Pilgrimage

The Hajj and Umrah are religious pilgrimages to Mecca, Saudi Arabia. Hajj only takes place from 8th-12th of Dhul Hijah, the last month of the Islamic year, while Umrah can be performed at any time. Approximately 3 million Muslims from over 180 countries make the Hajj every year. The Umrah pilgrims are estimated to be approximately 20 million every year with the projection of 30 million in 2030. The pilgrims should be educated on the general healthcare and communicable diseases' preventions.

All pilgrims should be up-to-date with routine vaccinations. The most current vaccination requirements are available from the Saudi Arabian Ministry of Health website (www.moh.gov.sa/en/). The recommended vaccines for Hajj and Umrah pilgrimage are also available at CDC website (https://wwwnc.cdc.gov/travel/yellowbook/2018/select-destinations/saudi-arabia-hajj-umrah-pilgrimage).

Compulsory Meningococcal Vaccine

The Saudi Ministry of Health requires all pilgrims to receive the meningococcal vaccine. Hajj and Umrah visas will not be issued without proof of vaccination. All adults and children aged more than 2 years must receive a single dose of quadrivalent A/C/Y/W135 vaccine. They must also show proof of vaccination on a valid International Certificate of Prophylaxis. They must have received the vaccine less than 2-3 years (depending on the brand administered*) and more than 10 days before arriving in Saudi Arabia. Meningococcal vaccination requirements are updated regularly by the Saudi Arabian authorities and can be found at www.moh.gov.sa/en/Hajj

Recommended vaccines for respiratory infections

Respiratory tract infections are common during Hajj, with pneumonia being the most common cause of hospital admission. These risks underscore the need for pneumococcal conjugate and/or polysaccharide vaccines for pilgrims aged ≥60 years and for younger travelers with comorbidities (See page 130).

The Scientific Committee for Influenza and Pneumococcal Vaccination of the Saudi Thoracic Society recommends the following before the Hajj season:

- All persons at ≥50 year are recommended to receive sequential vaccination before the Hajj or Umrah beginning with PCV13 followed by PPV23 at least 8 weeks later (ideally 1 year). If this is not possible, it is recommended to administer one dose of PPV23.

- Immunocompetent persons <50 years with risk factors are recommended to receive single dose PPV23 at least 3 weeks before the Hajj.

- Because of lack of evidence, it is not recommended to provide pneumococcal vaccines routinely to healthy persons aged <50 years.

Seasonal influenza vaccine is strongly recommended for all pilgrims (See page 95). Inactivated Influenza vaccine can be administered concurrently with pneumococcal polysaccharide vaccine.

Additional vaccinations and measures

The crowded conditions during Hajj increase the probability of respiratory pathogens transmission. Risk of tuberculosis transmission is estimated to be about 10% in those with high levels of exposure. Transmission of emerging pathogens e.g. Middle East respiratory syndrome (MERS) has also been documented in 2012. For further information, refer to the Saudi Arabian MOH website (https://www.moh.gov.sa/en/Hajj/HealthGuidelines/HealthGuidelinesDuringHajj/Pages/default.aspx).

In addition to the above vaccines, hepatitis A and B, influenza and typhoid vaccines are also recommended (Refer relevant sections).

Behavioural interventions such as hand hygiene, wearing a face mask, cough etiquette, social distancing, and contact avoidance may mitigate respiratory illness among pilgrims. Pre-travel advice about common respiratory conditions should include a general assessment for respiratory fitness, necessary vaccinations, and prescription of adequate supplies of portable respiratory medications (inhalers are easier to transport than nebulizers).

References

1. Alharbi N.S. Al-Barrak, A. M., Al-Moamary, M. S., Zeitouni, M. O., Idrees, M. M., Al-Ghobain, M. O., Al-Shimemeri, A. A. & Al-Hajjaj, M.S. (2016). The Saudi Thoracic Society pneumococcal vaccination guidelines-2016. Annals of Thoracic Medicine, 11(2): 93-102.
2. Kingdom of Saudi Arabia. Ministry of Health (2018). Health Requirements and Recommendations for Travelers to Saudi Arabia for Hajj and Umrah - 2018/1439H. https://www.moh.gov.sa/en/hajj/pages/healthregulations.aspx
3. US. Centers for Disease Control and Prevention (2018). Traveller's Health - Saudi Arabia: Hajj/Umrah Pilgrimage. https://wwwnc.cdc.gov/travel/yellowbook/2018/select-destinations/saudi-arabia-hajj-umrah-pilgrimage

Veterinarians And Animal Handlers

Table 21.11
Immunisation For Veterinarians and Animal Handlers

Category	Vaccines Recommended	When to Give	Comments
Personnel working exclusively with non-feral rodents and rabbits from approved sources and cold blooded vertebrates.	BCG (if Mantoux negative) Tetanus	Vaccination at time of employment. A tetanus booster is recommended every 10 years.	Health check-up at time of employment
Personnel working or exposed to feral animals and purpose bred laboratory animals from non approved sources and farm animals	BCG (if Mantoux negative) Tetanus	Vaccination at time of employment. A tetanus booster is recommended every 10 yrs.	Health check-up at time of employment
Personnel exposed to cats, dogs, feral animals from populations known to be potential carriers of rabies	BCG (if Mantoux negative) Tetanus Rabies	Vaccination at time of employment. A tetanus booster is recommended every 10 yrs. A rabies booster is recommended every 2 yrs.	
Personnel working with nonhuman primates	BCG (if Mantoux negative) Tetanus Measles	Vaccination at time of employment. A tetanus booster is recommended every 10 yrs.	Health check-up at time of employment.

Special Groups

Category	Vaccines Recommended	When to Give	Comments
Personnel involved in animal care for laboratory animals	BCG (if Mantoux negative) Tetanus	Vaccination at time of employment. A tetanus booster is recommended every 10 years.	Health check-up at time of employment.
Personnel with exposure to poultry, domestic, non domestic birds or pigs.	Influenza JE	Vaccination needed in case of an outbreak.	Note that the best protection against influenza is by having good personal hygiene and a healthy lifestyle. Workers handling birds should also take the general precautionary measures against avian influenza.

Malaysian Society of Infectious Diseases & Chemotherapy

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