Malaysian Society of Infectious Diseases and Chemotherapy

GUIDELINES FOR ADULT IMMUNISATION

2nd Edition
<table>
<thead>
<tr>
<th>Vaccination</th>
<th>19-21 yrs</th>
<th>22-26 yrs</th>
<th>27-49 yrs</th>
<th>50-59 yrs</th>
<th>60-64 yrs</th>
<th>≥65 yrs</th>
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</thead>
<tbody>
<tr>
<td>Influenza*</td>
<td>1 dose annually</td>
<td></td>
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</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Td/Tdap)*</td>
<td>Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs</td>
<td></td>
<td></td>
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<tr>
<td>Varicella*</td>
<td>2 doses</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Human papillomavirus (HPV) Female*</td>
<td>3 doses</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (HPV) Male*</td>
<td>3 doses</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster*</td>
<td>1 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella (MMR)*</td>
<td>1 or 2 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugate (PCV)*</td>
<td>1 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal polysaccharide (PPV)*</td>
<td>1 or 2 doses</td>
<td>1 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal*</td>
<td>1 or more doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A*</td>
<td>2 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B*</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib)*</td>
<td>1 or 3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 relevant section for more details
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## Introduction

### General Advice on Immunisation

### Vaccine-preventable Diseases

- Cholera
- Diphtheria, Tetanus, Pertussis (DTP)
- *Haemophilus influenzae* Type b Infections
- Hepatitis A
- Hepatitis B
- Human Papillomavirus Infections
- Influenza
- Japanese Encephalitis
- Measles, Mumps, Rubella (MMR)
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Abbreviations

ADR adverse drug reactions
AEFI adverse event following immunisation
AIDS acquired immunodeficiency syndrome
anti-HBc antibody to hepatitis B core antigen
anti-HBe antibody to hepatitis B e antigen
anti-HBs antibody to hepatitis B surface antigen
AOM acute otitis media
AVA anthrax vaccine adsorbed
BCG bacille Calmette-Guérin
CCID50 cell culture infectious dose 50%
CCVs cell culture vaccines
CI confidence interval
CIN cervical intraepithelial neoplasia
CRS congenital rubella syndrome
CSF cerebrospinal fluid
DNA deoxyribonucleic acid
DT diphtheria-tetanus (vaccine for use in children)
DTaP diphtheria and tetanus toxoids and acellular pertussis vaccine (pediatric formulation replaced DTP)
EIA enzyme immunoassay
eIPV enhanced inactivated polio vaccine
ELISA enzyme-linked immunosorbent assay
FHA filamentous haemagglutinin
FIM fimbriae (pertussis)
GBS Guillain-Barré syndrome
GP general practitioner
GVHD graft-versus-host disease
HAV hepatitis A virus
HBcAg hepatitis B core antigen
HBeAg hepatitis B e antigen
HBIG hepatitis B immunoglobulin
HBsAg hepatitis B surface antigen
HBV hepatitis B virus
HCW healthcare worker
HDCV human diploid cell vaccine (rabies)
HepA hepatitis A vaccine
HepB hepatitis B vaccine
HHE hypotonic-hyporesponsive episode
Hib Haemophilus influenzae type b
Hib-MenCCV Haemophilus influenzae type b-Meningococcal C conjugate vaccine
HIV human immunodeficiency virus
HPV human papillomavirus
HPV2 bivalent HPV vaccine
HPV4 quadrivalent HPV vaccine
HRIG human rabies immunoglobulin
HSCT haematopoietic stem cell transplant
HZ herpes zoster
HZV herpes zoster (Shingles) vaccine (formerly called ZOS)
ID intradermal
IgA/G/M immunoglobulin A/G/M
IIV inactivated influenza vaccine (formerly called TIV)
IM intramuscular
IPD invasive pneumococcal disease
IPV inactivated poliomyelitis vaccine
IS intussusception
ITP idiopathic thrombocytopenia purpura
IU international units
IV intravenous
JE Japanese encephalitis
JE-MB inactivated, mouse brain-derived Japanese encephalitis vaccine
LAIV live, attenuated influenza vaccine (nasal spray)
LT-ETEC heat-labile toxin producing enterotoxigenic *Escherichia coli*
MCV measles antigen-containing vaccines
MUC4 meningococcal conjugate vaccine (quadravalent)
MenACWY-CRM meningococcal conjugate vaccine
MenACWY-D meningococcal conjugate vaccine, quadrivalent
MenC meningitis C
MMR measles-mumps-rubella
MMRV measles-mumps-rubella-varicella
NHIG normal human immunoglobulin
NIP National Immunisation Program
NPCB National Pharmaceutical Control Bureau
NTHi non-typeable *Haemophilus influenzae*
OMP outer membrane protein
OPV oral poliomyelitis vaccine
PCECV purified chick embryo cell vaccine (rabies)
PCR polymerase chain reaction
PCV pneumococcal conjugate vaccine
PCV10 pneumococcal conjugate vaccine (10 valent)
PCV13 pneumococcal conjugate vaccine (13 valent)
PCV7 pneumococcal conjugate vaccine (7 valent)
PEP post-exposure prophylaxis
pH1N1 pandemic influenza A(H1N1) pdm09
PHN post-herpetic neuralgia
PI product information
PPV23 pneumococcal polysaccharide vaccine (23-valent)
PRN pertactin
PRP polyribosylribitol phosphate
PRP-OMP PRP conjugated to the outer membrane protein (of *Neisseria meningitidis*)
PRP-T PRP conjugated to tetanus toxoid
PT pertussis toxoid
PVRV purified vero cell-based vaccine
RCT randomised controlled trial
RIG rabies immunoglobulin
RNA ribonucleic acid
SC subcutaneous
SCID severe combined immunodeficiency
SIDS sudden infant death syndrome
SOT solid organ transplant
SSPE subacute sclerosing panencephalitis
TB tuberculosis
TCID50 tissue culture infectious dose 50%
Td tetanus & diphtheria vaccine (adult/adolescent formulation)
Tdap tetanus, diphtheria & acellular pertussis vaccine (adult/adolescent formulation)
TGA Therapeutic Goods Administration
TIG tetanus immunoglobulin
TST tuberculin skin test
TT tetanus toxoid
Ty21a live oral typhoid vaccine
VAR varicella vaccine
VLP virus-like particle
VNA (rabies) virus neutralising antibody
VPD vaccine-preventable disease
VV varicella vaccine
VZV varicella-zoster virus
WA Western Australia
WHO World Health Organization
ZIG zoster immunoglobulin
Immunication 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 practised. 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. Vaccine-preventable diseases are still commonly encountered in Malaysia. The Ministry of Health Malaysia data for 2011, showed that the incidence rates for measles, hepatitis B and pertussis were 5.42, 4.32, 0.86 per 100,000 population respectively. In Singapore, it has been reported that the proportion of influenza associated deaths was 11.3 times higher in persons aged 65 years and above. In the United States, nearly 50,000 adults die from vaccine-preventable diseases each year. Approximately 36,000 adults die from influenza, over 6,000 from invasive pneumococcal disease and 5,000 from hepatitis B. In contrast, less than 500 children die from vaccine-preventable diseases each year in the United States.

Adults require immunisation for various reasons. Even though they may have received immunisation as children, immunity can wane with age unless boosters are given regularly. In the United States, the risk of mortality from tetanus is highest among those aged 60 years and above. Vaccinating adults can help prevent infections (such as, pertussis) among young children with whom these adults have close contact.
Some vaccines like the shingles (herpes zoster) vaccine are meant only for adults above 60 years old. Adults may require immunisations when they travel, including some that may be mandatory due to circumstances. Sometimes, adults may also require immunisations which they have missed during childhood. Immunisations are also recommended for certain occupational groups (eg healthcare workers) and those with chronic underlying diseases (like cardiovascular and respiratory diseases).

The primary objective for developing 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 second edition of the Guidelines For Adult Immunisation and we hope that it will provide a useful resource for all doctors in Malaysia.
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: Yellow fever vaccine and some influenza vaccines should not be given. Recent data suggest that anaphylactic reactions with MMR vaccine are not associated with hypersensitivity to egg antigens but to other components of the vaccine (such as gelatine). Thus, children with egg allergy should still receive the MMR vaccination, as it is not a contraindication.

Several recently published reviews, guidelines and reports have indicated that the risk of anaphylaxis associated with influenza vaccination of egg-allergic patients is currently very low. Persons with egg allergy, including anaphylaxis, can be safely vaccinated with influenza vaccines that have less than 1µg of residual egg ovalbumin per dose. Due to changes in influenza vaccine manufacturing, the majority of influenza vaccines currently used contain less than 1µg of ovalbumin per dose. The product information of the vaccine to be given should be checked for the vaccine’s ovalbumin content prior to vaccine administration.
— **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.

— **Pregnancy:** There is no evidence that any live vaccine (including rubella and MMR) causes birth defects. However, since the theoretical possibility of foetal infection exists, live vaccines should generally be delayed until after delivery. 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 immunocompromised individuals (including the HIV-infected), due to extensive replication of the vaccine strain. For this reason, severely immunocompromised individuals (see section on Immunocompromised Patients, pg 165) 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 response than in immunocompetent individuals, a double dose may be required.
General Advice on Immunisation

● Other considerations:

  — Some patients with 22q11 deletion syndromes, including partial DiGeorge syndrome, may be able to receive live vaccines safely provided that they have no evidence of severe immunodeficiency.

  — 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 are likely to be safe in those receiving other immunomodulating drugs, like interferon. Deferral of immunisation may be suggested to avoid side-effects of the drugs being confused with reactions to vaccination.

● Live vaccinations should not be given to the following:

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

  — Patients with evidence of severe primary immunodeficiency or impaired immunological mechanism like hypogammaglobulinaemia.

Deferral of Immunisation

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

  — Individuals with immunosuppression from malignant disease or chemotherapy should not receive live attenuated vaccines until at least 6 months after chemotherapy has finished.
Patients who received a bone marrow transplant may be given live attenuated vaccines only after at least 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, should not be given during the 3 months following injection of immunoglobulin because the immune response may be inhibited.

The following are NOT contraindications to routine vaccinations:

- Minor self-limiting illness without fever.
- Asthma, eczema, or hay fever.
- Treatment with antibiotics or locally-acting (eg 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.
Route and Site of Administration

● By mouth:

— Sugar lumps, if used, should be prepared with oral polio vaccine (OPV) immediately before administration. Allowing them to stand at room temperature for any length of time may decrease the potency of the vaccine.

— If cholera and typhoid vaccines are 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 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 noses 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 and intramuscular injections:

— Most vaccines are given by intramuscular (IM) injections, rather than deep subcutaneous (SC) injections, 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 deltoïd area of the upper arm. The ventrogluteal area is an alternative injection site.

— IM injections should be given with a needle at a 90° angle to the skin and the skin should be stretched, not bunched. Deep SC injections should be given with a needle at a 45° 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).

● Intradermal injections:

— The BCG vaccine is ALWAYS given intradermally. The preferred site of injection is over the insertion of the left deltoïd 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.

— While the intramuscular 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 deltoïd muscle.
— The inactivated influenza vaccine administered by the intradermal route (Intanza®), is supplied in a micro-needle injection system that is held at right-angles to the skin. The device allows intradermal vaccination to be performed without the need for additional training.

— 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.

— 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).

● 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 of the buttock.

— Rabies immunoglobulin should be infiltrated into the site of the wound.
Figure 1.1
Techniques of Administration

a) Subcutaneous (SC) Injection

b) Intramuscular (IM) Injection

c) Intradermal (ID) Injection
### General Advice on Immunisation

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

### Table 1.1
Injection Routes for Common Vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria, tetanus, pertussis (DTaP, DT, Tdap, Td)</td>
<td>0.5mL</td>
<td>IM</td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib)</td>
<td>0.5mL</td>
<td>IM</td>
</tr>
<tr>
<td>Hepatitis A (Hep A)</td>
<td>≤18 yrs: 0.5mL, &gt;18 yrs: 1.0mL</td>
<td>IM</td>
</tr>
<tr>
<td>Hepatitis B (Hep B)</td>
<td>&lt;20 yrs: 0.5mL, ≥20 yrs: 1.0mL</td>
<td>IM</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>0.5mL</td>
<td>IM</td>
</tr>
<tr>
<td>Influenza, trivalent inactivated (TIV)</td>
<td>0.5mL</td>
<td>Intranasal Spray</td>
</tr>
<tr>
<td>Measles, mumps, rubella (MMR)</td>
<td>0.5mL</td>
<td>SC</td>
</tr>
<tr>
<td>Meningococcal conjugate (MCV)</td>
<td>0.5mL</td>
<td>IM</td>
</tr>
<tr>
<td>Meningococcal polysaccharide (MPSV)</td>
<td>0.5mL</td>
<td>SC</td>
</tr>
<tr>
<td>Pneumococcal conjugate (PCV)</td>
<td>0.5mL</td>
<td>IM</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide (PPSV)</td>
<td>0.5mL</td>
<td>IM or SC</td>
</tr>
<tr>
<td>Polio, inactivated (IPV)</td>
<td>0.5mL</td>
<td>IM or SC</td>
</tr>
<tr>
<td>Rotavirus (RV)</td>
<td>2.0mL</td>
<td>Oral</td>
</tr>
<tr>
<td>Varicella (Var)</td>
<td>0.5mL</td>
<td>SC</td>
</tr>
<tr>
<td>Zoster (Zos)</td>
<td>0.65mL</td>
<td>SC</td>
</tr>
</tbody>
</table>

**Combination Vaccines**

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP + Hib + IPV</td>
<td>0.5mL</td>
<td>IM</td>
</tr>
<tr>
<td>DTaP + Hib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTaP + IPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HepA + HepB (Twinrix®)</td>
<td>≥18 yrs: 1.0mL</td>
<td>IM</td>
</tr>
</tbody>
</table>
**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.

<table>
<thead>
<tr>
<th>Age</th>
<th>Needle Length</th>
<th>Injection Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (1-12 mos)</td>
<td>⅝ in</td>
<td>Fatty tissue over anterolateral thigh muscle</td>
</tr>
<tr>
<td>Children (12 mos or older), adolescents,</td>
<td>⅝ in</td>
<td>Fatty tissue over anterolateral thigh muscle or fatty tissue over triceps</td>
</tr>
<tr>
<td>and adults</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Age</th>
<th>Needle Length</th>
<th>Injection Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns (1st 28 days)</td>
<td>⅝ in*</td>
<td>Anterolateral thigh muscle</td>
</tr>
<tr>
<td>Infants (1-12 mos)</td>
<td>1 in</td>
<td>Anterolateral thigh muscle</td>
</tr>
<tr>
<td>Toddlers (1-2 yrs)</td>
<td>1-1¼ in</td>
<td>Anterolateral thigh muscle or deltoid muscle of arm</td>
</tr>
<tr>
<td></td>
<td>⅝ -1 in*</td>
<td></td>
</tr>
<tr>
<td>Children &amp; teens (3-18 yrs)</td>
<td>⅝ -1 in*</td>
<td>Deltoid muscle of arm or anterolateral thigh muscle</td>
</tr>
<tr>
<td></td>
<td>1-1¼ in</td>
<td></td>
</tr>
<tr>
<td>Adults (19 yrs or older)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male or female less than 59kg</td>
<td>⅝-1 in*</td>
<td>Deltoid muscle of arm</td>
</tr>
<tr>
<td>Female 59-92kg</td>
<td>1-1½ in</td>
<td>Deltoid muscle of arm</td>
</tr>
<tr>
<td>Male 59-118kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female over 92kg</td>
<td>1½ in</td>
<td>Deltoid muscle of arm</td>
</tr>
<tr>
<td>Male over 118kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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.*
Post Vaccination

- Recipients of vaccines should remain in the vicinity for at least 15 minutes until they appear to have recovered from the procedure. The area should be close enough so that the vaccinated person can be observed and medical treatment 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. As 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 0.5-1.0mL 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 necessary, begin cardio-pulmonary resuscitation (CPR).
  — Chlorpheniramine maleate 2.5-5.0mg may be given intravenously. Hydrocortisone 100mg intravenously may also be given 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 three 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 eg 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.

- Reconstituted vaccines 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
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.
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.

- Unused vaccines in 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.
- Problems of combination:
  - Side-effects may be more frequent and worse.
  - Reduced antibody response due to interference.
- Compatible combinations (must be given at different sites and in different syringes unless otherwise indicated by the manufacturer):
  - BCG + yellow fever
  - BCG + DTaP + oral polio
  - BCG + measles + yellow fever + tetanus
  - DTaP + hepatitis B + *Haemophilus influenzae* type b (Hib)
  - DTaP + hepatitis B + IPV
  - DTaP + yellow fever
  - DTaP + oral polio + yellow fever + measles
  - DTaP + BCG + yellow fever + measles
  - DT + IPV
  - Hepatitis A + Hepatitis B
  - Hepatitis B + *Haemophilus influenzae* type b (Hib)
  - Measles + mumps + rubella + VZV
● Not encouraged:
  – DT + typhoid + oral polio
  – Cholera + yellow fever

**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 and 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 of 4 weeks’ interval.

● 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 below).

Table 1.3
Intervals Between Vaccines and Immunoglobulin Preparations Not Administered Simultaneously

<table>
<thead>
<tr>
<th>Vaccine Products</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between live vaccine to immunoglobulin</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Between immunoglobulin to live vaccine</td>
<td>3 months</td>
</tr>
<tr>
<td>Between inactivated vaccine to immunoglobulin</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

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 Control Bureau, Ministry of Health Malaysia. All reports received will be assessed for causality and presented in the Malaysian Adverse Drug Reaction Advisory Committee, the secretariat 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, healthcare professionals can contact the National Centre for Adverse Drug Reaction Monitoring, National Pharmaceutical Control Bureau (NPCB):
  - By phone: 03-78835400 (ext: 8464/8465/8470)
  - Via the online website: https://www.bpfk.gov.my/quest2/madrac%20-%20reporting%20online.htm
  - Or mail to:
    National Pharmaceutical Control Bureau
    Lot 36, Jalan Universiti,
    46730 Petaling Jaya,
    Selangor, Malaysia

- The National Pharmaceutical Control Bureau has developed a Guideline for Pharmacovigilance of Vaccines in Malaysia available at the official website: www.bpfk.gov.my. Please refer to the guideline for further details.

References

8. Immunisation Guidelines 2006. Dubai Health Authority, Dubai
Introduction

Cholera is an important public health problem for many countries and is estimated that the disease kills between 75,000 and 120,000 people every year. It is an acute enteric infection caused by the ingestion of the bacteria *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 have 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 and those who are immunocompromised taking the vaccine. However, it should only be used if the benefits outweigh the risk.
Vaccines

- **Shanchol®**
  - It is a bivalent vaccine protecting both against *V. cholerae* O1 and O139. It does not contain the bacterial toxin B-subunit and thus does not require any buffer for administration. Shanchol® provided 67% protection against clinically significant *V. cholerae* O1 cholera in an endemic area for at least 2 years after vaccination. Protection was seen both in children vaccinated at ages under 5 years and in older persons as well.

- **Dukoral® (WC/rBS)**
  - It consists 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.

Vaccines Available in Malaysia

- **Shanchol®** (Killed bivalent [O1 & O139] whole cell oral cholera vaccine)
  - Sanofi Pasteur*

- **Dukoral®** (Cholera and ETEC-diarrhoea)
  - Johnson & Johnson

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
Table 2.1
Vaccines Available in Malaysia

<table>
<thead>
<tr>
<th>Commercial name</th>
<th><strong>Shanchol</strong>® (variant WC)</th>
<th><strong>Dukoral</strong>® (WC/rBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protection against</td>
<td><em>V. cholerae O1 and O139 for &gt;50% for 2 years</em></td>
<td><em>V. cholerae O1 for &gt;50% for 2 years</em></td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Children &lt;1 year</td>
<td>Children &lt;2 years</td>
</tr>
<tr>
<td>Presentation</td>
<td>Oral suspension (vaccine)</td>
<td>Oral suspension (vaccine) and effervescent granules (buffer)</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>2 years</td>
<td>3 years</td>
</tr>
<tr>
<td>Storage</td>
<td>Cold chain (2-8°C)</td>
<td>Cold chain (2-8°C)</td>
</tr>
<tr>
<td>Stability at ambient temperature</td>
<td>Stability tests on-going</td>
<td>1 month at 37°C</td>
</tr>
<tr>
<td>Administration course</td>
<td>2 doses, (min) 1 to (max) 6 weeks apart</td>
<td>2 doses, (min) 1 to (max) 6 weeks apart</td>
</tr>
<tr>
<td>Amount of drinking water needed/dose</td>
<td>None</td>
<td>150mL for adults and children &gt;6 years 75mL for children 2-6 years</td>
</tr>
</tbody>
</table>

Mode of Administration

- **Shanchol**®
  - 2 doses orally are given at an interval of 2 weeks.
  - The vaccine is prepared in single-dose vials. It should be shaken prior to administration.
  - The shelf-life is 2 years at a temperature between 2-8°C.
  - DO NOT FREEZE the vaccine. Discard the vaccine if it is frozen.
● **Dukoral®**
  
  — 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 orally are given 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.
  
  — After reconstituted, the vaccine should be drunk within 2 hours.

**Contraindications and 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 had been reported as well.

— To date, the National Adverse Drug Reactions Monitoring Centre, NPCB has not received any AEFI reports for cholera vaccines.

**References**

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 an adherent pseudomembrane. 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.

Humans are the only known reservoir of *C. diphtheriae*. The disease is spread by aerosol transmission or by direct contact with skin lesions or articles soiled by infected persons. Carriers are important in disease transmission as natural or vaccine induced immunity does not prevent carriage. Diphtheria occurs primarily among unvaccinated or inadequately vaccinated individuals.

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 has been no diphtheria case in 2011 and 2012, since the 3 cases reported in 2010.

Diphtheria antitoxin is available in 10 major hospitals for treatment of diphtheria cases. The list is as shown below.

- Hospital Kuala Lumpur
- Hospital Pulau Pinang
- Hospital Sultanah Nur Zahirah, Terengganu
- Hospital Sultanah Aminah, Johor Bahru
- Hospital Umum Kuching, Sarawak
- Hospital Wanita & Kanak-kanak, Kota Kinabalu, Sabah
- Hospital Sibu, Sarawak
- Hospital Miri, Sarawak
- Hospital Duchess of Kent, Sandakan, Sabah
- Hospital Tawau, Sabah
Vaccines

- This is a toxoid-derived vaccine that is adsorbed onto an adjuvant (aluminium salt, usually aluminium phosphate) to increase its immunogenicity. The diphtheria vaccine is present in combination with tetanus and pertussis. There are several formulations available (DTaP, DTP, Tdap, DT and Td). DTaP, DTP and DT are given to children younger than 7 years of age while Tdap and Td are used in adolescents and adults.

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

- **Adacel®** (Tdap; tetanus-diphtheria-acellular pertussis)
  - Sanofi Pasteur*
- **Adacel® Polio** (Tdap-IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)
  - Sanofi Pasteur*
- **Boostrix®** (Tdap; tetanus-diphtheria-acellular pertussis)
  - GlaxoSmithKline
- **Boostrix-Polio®** (Tdap-IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)
  - GlaxoSmithKline

Note: No Td-containing vaccine available in Malaysia. Only DT or DTP for paediatric population.

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
Mode of Administration

- The dose is 0.5mL given by intramuscular injection.
- **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:** Booster dose of Tdap vaccine is usually given at 10 and 20 years after the primary course. The booster dose of diphtheria-containing vaccine is essential for maintaining immunity to diphtheria (as well as tetanus and pertussis).

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 Adverse Drug Reactions Monitoring Centre, NPCB include injection site reactions such as injection site swelling and fever. Cases of febrile seizure and convulsions have also been reported in children.
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 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.

References

Tetanus

Introduction

Tetanus is caused by *Clostridium tetani* which produces a potent toxin that has 2 components, ie tetanospasmin (a neurotoxin) and tetanolysin (a haemolysin). The organisms usually gain entry through open wounds and lacerations or via penetrating injuries. 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.

In Malaysia, tetanus is rare with the incidence rate in 2012 reported as 0.03 per 100,000 population. Tetanus in adults tends to occur primarily in the older age group who were never vaccinated or who were vaccinated in the distant past. As tetanus is associated with apparently minor or trivial injury, especially in the elderly, active immunisation is thus important for its prevention.

In Malaysia, maternal and neonatal tetanus has been eliminated (less than 1 per 1000 live birth) since 1990 when the elimination goal was announced at the World Summit for Children.

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 single antigen preparation (TT), combined with diphtheria toxoid (DT, Td), and combined with both diphtheria toxoid and pertussis (DT/DTP/DTaP/Tdap).
- 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

● Tetanus toxoid
  – **Tetavax®** (Adsorbed tetanus vaccine)*
    – Sanofi Pasteur*
  – **TT Vaccine®** (Adsorbed tetanus vaccine)
    – Propharm/Bio Farma
  – **Tetanus Toxoid Vaccine®** (Adsorbed tetanus vaccine)
    – Serum Institute of India/SM Pharmaceuticals

● Combination vaccines
  – **Adacel®** (Tdap; tetanus-diphtheria-acellular pertussis)
    – Sanofi Pasteur*
  – **Adacel® Polio** (Tdap-IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)
    – Sanofi Pasteur*
  – **Boostrix®** (Tdap; tetanus-diphtheria-acellular pertussis)
    – GlaxoSmithKline
  – **Boostrix-Polio®** (Tdap-IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)
    – GlaxoSmithKline

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
# Registered in Malaysia but not marketed. May be made available with request
● Tetanus Immune Globulin (TIG)

  – Sero-Tet® (Human tetanus immune globulin)
    – Propharm/Green Cross

  – Igantet® (Human antitetanus Ig)
    – Grifols

Mode of Administration

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

● Primary vaccination in adults: 3 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: Booster dose of Tdap vaccine is usually given at 10 and 20 years after the primary course. All adults who reach the age of 50 years without having received a booster dose Td in the previous 10 years should receive a further tetanus booster dose.

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. The recommended schedule is 0, 4 weeks, and 6 through 12 months. Tdap should replace 1 dose of Td, preferably between 27 and 36 weeks gestation to maximise the maternal antibody response and passive antibody transfer to the infant.

• 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).
Table 3.1
Guide to Tetanus Prophylaxis in Wound Management

<table>
<thead>
<tr>
<th>History of tetanus vaccination</th>
<th>Time since last dose</th>
<th>Type of wound</th>
<th>Tdap, DTaP combinations, DT, Tdap (as appropriate)</th>
<th>Tetanus immunoglobulin* (TIG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 doses</td>
<td>&lt;5 yrs</td>
<td>Clean minor wounds</td>
<td>No No</td>
<td>No No#</td>
</tr>
<tr>
<td>&gt;3 doses</td>
<td>5-10 yrs</td>
<td>Clean minor wounds</td>
<td>No Yes</td>
<td>No No#</td>
</tr>
<tr>
<td>&gt;3 doses</td>
<td>&gt;10 yrs</td>
<td>Clean minor wounds</td>
<td>Yes Yes</td>
<td>No No#</td>
</tr>
<tr>
<td>&lt;3 doses or uncertain§</td>
<td>Clean minor wounds</td>
<td>Yes Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* 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 clean minor 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.

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 *C. 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.

References


11. Talbot EA, Brown KH, Kirkland KB, et al. 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 2010;28:8001-7
Pertussis

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 rate of pertussis is reported to be less than 1 per 100,000 population for the past 20 years. There was however an increase of pertussis cases from 46 cases in 2010 to 249 cases in 2011. This increase was mainly contributed by the availability of PCR as a confirmatory test, which is more sensitive compared with detection of the bacteria by culture.

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.
Vaccines

- Pertussis vaccine is available only in combination with diphtheria, tetanus and other antigens.

- Tdap is the adult formulations of diphtheria, tetanus and acellular pertussis containing vaccine. Tdap contains substantially lesser amounts of diphtheria toxoid and pertussis antigens than the child formulation.

- There are a number of acellular pertussis containing vaccines that contain 2 or more purified components of *Bordetella pertussis*. 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

- **Adacel®** (Tdap; tetanus-diphtheria-acellular pertussis)
  – Sanofi Pasteur*

- **Adacel® Polio** (Tdap-IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)
  – Sanofi Pasteur*

- **Boostrix®** (Tdap; tetanus-diphtheria-acellular pertussis)
  – GlaxoSmithKline

- **Boostrix-Polio®** (Tdap-IPV; tetanus-diphtheria-acellular pertussis-inactivated polio)
  – GlaxoSmithKline

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
Mode of Administration

- The dose of pertussis-containing vaccines is 0.5mL to be given by IM injection.
- Tdap vaccine is recommended for a tetanus and diphtheria booster at 50 years of age. There is currently insufficient evidence to recommend routine 10-yearly booster doses of Tdap vaccine for all adults, apart from those who meet the criteria of special risk groups (see section on Special Groups, pg 156)

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, NPCB include injection site reactions such as injection site swelling and fever. Cases of febrile seizure and convulsions had also been reported in children.

**Target Groups in Malaysia**

• All adults aged 50 years and above.
• Adults aged >65 years, if they have not received the booster dose in the previous 10 years.
• Persons in contact with infants and others at increased risk from pertussis*, eg:
  – Pregnant women.
  – Adult household contacts and carers of infants less than 6 months of age.
  – Staff working in early childhood education and care (kindergarten and nursery).

*Note: A booster dose of Tdap is recommended every 10 years for this group of people.

**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.
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.

References

1. Booy R, Van der Meeren O, Ng SP, et al. A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix™) is immunogenic and well tolerated in adults. Vaccine 2010; 29:45-50
Introduction

*Haemophilus influenzae* is a pleomorphic, gram negative coccobacillus. Many pathogenic strains of *H. influenzae* have a polysaccharide capsule and can be distinguished into 6 serotypes (a-f). Uncapsulated strains are non typeable.

The most virulent strain is *H. influenzae* type b (Hib). Hib infections are primarily diseases of childhood as adults are protected by naturally acquired antibodies. Hib causes more than 95% of invasive diseases in children. These infections include bacteremia, meningitis, cellulitis, epiglottitis, septic arthritis, pneumonia and empyema. Less common infections are endophthalmitis, urinary tract infection, abscesses, cervical adenitis, glossitis, osteomyelitis and endocarditis.

The World Health Organization estimated that, in year 2000, Hib caused 2-3 million cases of serious disease, notably pneumonia and meningitis, and 386,000 deaths in young children. The introduction of the Hib vaccine has led to dramatic decreases in the incidence, morbidity and mortality of Hib infections.

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

- The Hib vaccine is derived from the polyribosylribitol phosphate (PRP) capsule of the bacteria. The capsule of Hib is a major virulence factor for the organism. The antibody to PRP is the primary contributor to immunity, and increasing levels of antibody are associated with decreasing risk of invasive Hib disease. 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 is poor in children less than 18 months. So as to overcome this, PRP is conjugated with a T cell dependent protein antigen, like diphtheria toxoid – hence the term, conjugate vaccine.

Vaccines Available in Malaysia

- Hiberix® (*H. influenzae* type b)
  - GlaxoSmithKline

Mode of Administration

- Hib vaccines are administered subcutaneously or intramuscularly. Upper arm or anterolateral thigh sites are recommended to minimise the risk of local reactions.

- In children, primary immunisation comprises 3 doses given during the first 6 months. 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. (see section on Special Group, pg 156).
Co-administration with Other Vaccines

- Hib vaccines can be given at the same time as other vaccinations, such as measles, mumps, rubella (MMR), meningococcal C (MenC) or hepatitis B (Hep B), but should be injected at an alternative site and preferably in a different limb.

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 National Adverse Drug Reactions Monitoring Centre, NPCB 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:
  - **Splenectomy patients**: For those who have not received or completed Hib immunisation in childhood – 1 dose 2 weeks before a planned splenectomy or as soon as possible after an emergency splenectomy.
  - Recipients of bone marrow transplants – 3 doses at 12, 14 and 18 months after transplantation.

Evidence for Effectiveness

- There is good evidence that the introduction of Hib vaccination in children has resulted in dramatic decreases in the incidence of Hib disease. Countries which have introduced mass immunisation have witnessed near elimination of invasive Hib infections. There is however less evidence of efficacy in adults.

References

2. Haemophilus b Conjugate Vaccines for Prevention of Haemophilus influenza type b Disease Among Infants and Children Two Months of Age and Older recommendations of the ACIP. MMWR, January 11, 1991 / 40(RR01):1-7
Introduction

Hepatitis A (formerly known as “infectious hepatitis”) 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, difference in surveillance 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 tremendously from 11.65 (1988) to 9.16 (1991) and 4.72 (1997) 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 (ie 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 vaccines include HAV antigen and most contain aluminium hydroxide or aluminium hydroxyphosphate as adjuvant. They are available in paediatric and adult formulations.

**Vaccines Available in Malaysia**

- **Avaxim** (Hepatitis A) – Sanofi Pasteur*
- **Vivaxim** (Hepatitis A and typhoid) – Sanofi Pasteur*
- **Epaxal®** (Hepatitis A) – Crucell/Propharm
- **Havrix®** (Hepatitis A) – GlaxoSmithKline
- **Twinrix®** (Hepatitis A and B) – GlaxoSmithKline
- **Vaqta®** (Hepatitis A) – Merck Sharp & Dohme

**Mode of Administration**

- The primary vaccination consists of 1 single dose of vaccine followed by a booster injection preferably 6-12 months after the 1st vaccination.
- 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 higher risk of local reaction including injection site nodule.

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
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 (including Malaysia), 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 are local site reactions such as injections site pain and swelling. Systemic reactions as fever, fatigue and urticaria have also been reported.
Target Groups in Malaysia

- Travellers 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.
- Illicit 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

Introduction

Hepatitis B was originally known as “serum hepatitis”. It 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 and 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 1 of the 10 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 is 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. A seroprevalence study on HBsAg on new students enrolled in undergraduate and postgraduate courses at one of the local universities revealed only 0.2% of those born in or after 1989 were seropositive. 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 children up to about 24 years of age.
Vaccines

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

Vaccines Available in Malaysia

- **Euvax-B** (Hepatitis B)  
  - Sanofi Pasteur*

- **Engerix-B®** (Hepatitis B)  
  - GlaxoSmithKline

- **HBvaxPRO®** (Hepatitis B)  
  - Merck Sharp & Dohme

- **Hepavax-Gene TF®** (Hepatitis B)  
  - Berna Biotech/Propharm

- **Heberbiovac HB®** (Hepatitis B)  
  - Centro Nacional De Biopreparados (CNB)/DNA Biosciences

- **Twinrix®** (Hepatitis A and B)  
  - GlaxoSmithKline

- **Hepabig Injection®**  
  - Green Cross Corporation/Propharm

- **Hepatitis-B Vaccine®**  
  - Serum Institute of India/SM Pharmaceutical

- **Shanvac®** (Hepatitis B)  
  - Shanta Biotechnics Limited/Sanofi Pasteur*

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
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, travellers to endemic regions and close contacts of infected subjects), the 3-dose or the accelerated schedule should be used.
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 lost 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, NPCB are local site reactions such as injection site pain and induration, rash, fever, vomiting and body discomfort.
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.
  - Travellers 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 (HCWs). 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 management must make serious efforts to improve the coverage.

- Pre-vaccination serologic 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 144).
Evidence for Effectiveness

- Anti-HBs is the only easily measurable correlate of the 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

5. MOH Malaysia. Hepatitis B Seroprevalence Study Among Children Year 3 and 4. 2009 (unpublished)
Introduction

Human papillomaviruses (HPVs) are small, non-enveloped, double-stranded DNA viruses. There are more than 100 HPV genotypes 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. Other HPV types, including types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 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 some may result in lesions that include cutaneous warts, genital warts, respiratory papillomatosis (low-risk HPV types) and dysplasias, and cancers of the cervix, vulva, vagina, penis, anus, the oral cavity and oropharynx (high-risk HPV types). HPV types 16 and 18 cause 70% of cervical cancers. The low-risk HPV types 6 and 11 cause 90% of anogenital warts and almost all recurrent respiratory papillomatosis. Most genital HPV infections are self-limiting with complete recovery but in 20% of infections, the virus persists. Persons with persistent HPV infection are at risk of developing HPV-associated cancers.

Vaccination with the bivalent (types 16 and 18) HPV vaccine is recommended for protection against cervical, vulvar and vaginal cancers in females, while the quadrivalent (types 16, 18, 6 and 11) will also protect both females and males from anal cancers, precancers and genital warts. It is important to get all 3 doses of HPV vaccine to get the full benefits.

WHO’s Strategic Advisory Group of Experts (SAGE), on vaccines and immunisation recommended the use of HPV vaccine in November 2008. WHO published a complete position paper in April 2009 as well as a detailed background paper that summarised the evidence.
Regular cervical screening, which detects histopathological changes, remains an important preventive measure against cervical diseases. Vaccination protects against most, but not all, HPV types that cause cervical cancer. There are also other infections and risk factors associated with cervical cancer which is the 3rd most common cancer among women in Malaysia after breast and colorectal cancers. Likewise, cervical screening is not an alternative to HPV vaccination. Both are recommended. 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 behaviors (such as condom use).

HPV vaccines are routinely recommended for females and males aged 11 or 12 years. The vaccine series can be started at 9 years of age. Vaccination is also recommended for females aged 13-26 years and males aged 9-26 years (for Gardasil® only) years who were not vaccinated previously or did not complete the vaccination series. The decision to vaccinate older adolescents and adults should follow an assessment of the potential benefits, based on their previous HPV exposure and future risks of HPV exposure.

**Vaccines**

- 2 HPV vaccines are registered for use. The vaccines are produced from non-infectious HPV virus-like particles (VLPs) developed through recombinant DNA technologies. Only the quadrivalent vaccine is registered for use in males.

  - **Cervarix®** – GlaxoSmithKline
    - Bivalent HPV vaccine (HPV2).
    - Contains the major capsid (L1) protein of HPV types 16 and 18.
Each 0.5mL monodose vial or pre-filled syringe contains 20μg HPV-16 L1 protein and 20μg HPV-18 L1 protein, adjuvanted with AS04 (comprising 0.5mg aluminium hydroxide and 50μg 3-O-desacyl-4'-monophosphoryl lipid A).

Approved for use in females 9-25 years to help protect against cervical cancer.

— **Gardasil®** – Merck Sharpe & Dohme

Quadrivalent HPV vaccine (HPV4).

Contains the major capsid (L1) protein of HPV types 6, 11, 16 and 18.

Each 0.5mL monodose 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. It may also contain yeast proteins.

Approved for use in females aged 9-26 years to protect against cervical cancer and to prevent genital warts and anal cancers, and in males aged 9-26 years to prevent genital warts and anal cancers.

**Vaccines Available in Malaysia**

— **Cervarix®** (Human papillomavirus vaccine types 16 & 18)
  – GlaxoSmithKline

— **Gardasil®** (Human papillomavirus vaccine types 6,11,16 & 18)
  – Merck Sharp & Dohme
Mode of Administration

- The dose of both types of HPV vaccines is 0.5mL, administered by intramuscular injections, as a 3-dose schedule over a 6-month period. The 2nd and 3rd doses should be given 1-2 and 6 months after the 1st dose. The possible need for booster doses is not yet established. The minimum interval between the 1st and 2nd dose is 4 weeks. The minimum interval between the 1st and 3rd dose is 24 weeks.

- If scheduled doses have been missed or interrupted, there is no need to repeat earlier doses. The missed dose(s) should be given as soon as is practicable. Every effort should be made to complete a 3-dose schedule for effective protection.

- Currently, no clinical data is available on safety, immunogenicity or efficacy of the 2 HPV vaccines when used interchangeably. It is recommended that an HPV vaccination course commences with 1 vaccine and, wherever possible, be completed with that vaccine according to its 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 -18 if a total of 3 doses of HPV vaccine have been given, provided the minimum interval requirements between the doses are satisfied.

Co-administration with Other Vaccines

- Co-administration of a different inactivated or live vaccine, either simultaneously or at any time, before or after HPV vaccine is permitted because the HPV vaccines are not live vaccines. Both HPV vaccines can be administered with other vaccines at the same visit, using separate syringes and different injection sites.
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 bivalent vaccine in prefilled syringes is contraindicated for persons with anaphylactic latex allergy.
    - The quadrivalent vaccine is contraindicated for persons with a history of anaphylaxis to yeast.

- HPV vaccines should not be given to:
  - Those with moderate or severe acute illnesses. Wait until the illness improves before getting vaccinated.
  - Pregnant women. Although the vaccine has not been causally associated with adverse pregnancy outcomes or adverse effects on the developing foetus, data on vaccination in pregnancy are limited.

- HPV vaccines can be given 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.
Human Papillomavirus (HPV)

- Studies have shown no serious safety concerns and deem both HPV vaccines as safe. Common, mild adverse effects reported during the studies included pain, redness or swelling where the injection was given, fever, fatigue, headache, muscle or joint pain. Studies showed that serious adverse effects following the bivalent vaccine were similar in the vaccine and control groups. Post licensure data indicate that adverse events from the quadrivalent vaccine 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 Adverse Drug Reactions Monitoring Centre, NPCB are consistent with the studies which include pain, redness or swelling at the injection site, fever, fatigue, headache, muscle and joint pains.

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

- Life-threatening allergic reactions from vaccines are very rare. If they do occur, it would be 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 10-13 years before potential exposure to HPV through sexual activity. Where possible, 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).

Recommendations

● For females:
  – Girls aged 11-12 years should receive the vaccine series.
  – Girls as young as 9 years can receive the vaccine.
  – Girls and women aged 13-26 years:
    ✗ Who have not received the HPV vaccine in the past should be given a series of 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 quadrivalent vaccine series.
  – Boys as young as 9 years can receive the vaccine.
  – Boys and men aged 13-21 years:
    ✗ Who have not received the HPV vaccine in the past should be given a series of 3 doses.
    ✗ Who have not completed the full vaccine series should catch up on the missed doses.
Human Papillomavirus (HPV)

— Men aged 22-26 years:
   - Who have not received the HPV vaccine in the past may still be given the series of 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).

- For immunocompromised individuals:
  — Vaccination is recommended for adult men and women who are immunocompromised (for instance, 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.

Implications for Healthcare Workers (HCWs)

- Healthcare workers should follow the recommendations for adults based on age or other individual risk factors.

Evidence for Effectiveness

- Both vaccines are safe and have high efficacy against HPV 16- and 18-related cervical pre-cancer lesions. The quadrivalent (HPV4) vaccine also has high efficacy against HPV 6- and HPV 11-related genital warts and anal cancer, as well as HPV 16- and 18-related vaginal and vulvar pre-cancer lesions. The consistency of at least 5-6 years of observations strongly suggests that similar high rates of protection can be expected against cervical cancer.
• Immunogenicity studies of both vaccines have been conducted in girls aged 9-15 years. Over 99% of the vaccinated girls in these studies developed antibodies after vaccination. For the quadrivalent vaccine, immunogenicity data in males also showed high seroconversion rates for all 4 HPV types.

• The main efficacy study of the bivalent 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 the bivalent HPV vaccine showed that more than 99% of females developed HPV 16 and 18 antibody response 1 month after completing the 3-dose series.

• The main efficacy studies of the quadrivalent 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. 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 the bivalent vaccine in males has not been assessed to date.

• Current studies indicate that the vaccines are effective and suggest that vaccine protection is long-lasting. Recent data from long-term population-based follow-up studies indicate that protection lasted up to 9 years after vaccination and protective antibody levels are predicted to remain well above the natural infection level for at least 20 years.
References

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3. Centers for Disease Control and Prevention Recommendations on the use of quadrivalent human papillomavirus vaccine in males--Advisory Committee on Immunisation Practices (ACIP), 2011. MMWR 2011; 60(50):1705-8


Influenza is caused by an orthomyxovirus and is characterised by the abrupt start of fever, sore throat, headache, myalgia, chills, anorexia, and extreme fatigue with cough often starting 1 day after other symptoms. Major symptoms generally last an average of 7 days. The presence of cough and temperature are the best predictors of influenza illness in adults and children during periods of influenza circulation. A minority of patients may experience fatigue for months. In the elderly, fever may be absent while the presenting signs may include anorexia, lassitude or confusion.

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 often is fatal.

Influenza vaccines form the mainstay of public health and personal protection against infection by the currently circulating seasonal influenza viruses. Every year, WHO will update the latest recommended vaccine compositions for both the Northern and Southern hemispheres. Since the late 1970s, this has required the use of a trivalent vaccine, consisting of 2 influenza A viruses and 1 influenza B virus. However, since early 2000, a second lineage of B viruses that are quite distinct has regularly circulated in many countries with only low levels of cross protection between the 2 lineages. The difficulties in determining which B lineage will circulate and matching this with the vaccine to be administered some 6-9 months later have led to an increasing interest in the development of quadrivalent influenza vaccines, containing 2 influenza B viruses representing both lineages.
Vaccines

● Trivalent vaccines

  – **Vaxigrip** (Inactivated influenza vaccine) – Sanofi Pasteur*
  
  – **Intanza**\(^\text{®}\) (Inactivated influenza vaccine) – Sanofi Pasteur*
  
  – **Agrippal S1**\(^\text{®}\) (Inactivated influenza vaccine) – Novartis
  
  – **Fluarix**\(^\text{®}\) (Inactivated influenza vaccine) – GlaxoSmithKline
  
  – **Influvac**\(^\text{®}\) (Inactivated influenza vaccine) – Abbott
  
  – **Fluvax**\(^\text{®}\) (Inactivated influenza vaccine) – CSL
  
  – **Inflexal V**\(^\text{®}\) (Adjuvanted influenza vaccine) – Crucell/Propharm

● Adults aged ≥65 years

  – **Fluzone High-Dose** (Inactivated influenza vaccine) 
    – Sanofi Pasteur*
  
  – **Fluad** (Trivalent vaccine adjuvanted with MF59C.1 which contains squalene and polysorbate 80) 
    – Novartis

● Vaccines for intradermal administration

  – **Intanza 9μg**\(^\text{®}\) (For adults aged 18-59 years) – Sanofi Pasteur*
  
  – **Intanza 15μg**\(^\text{®}\) (Each 0.1mL pre-filled purpose-designed Micro-Injection System for adults aged ≥60 years) – Sanofi Pasteur*

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
● Quadrivalent vaccines

   – FluQuadri™ (Inactivated influenza vaccine)
     – Sanofi Pasteur*

   – Fluarix Quadrivalent® (Inactivated influenza vaccine)
     – GlaxoSmithKline

Vaccines Available in Malaysia

● Vaxigrip – Sanofi Pasteur*

● Intanza® – Sanofi Pasteur*

● Agrippal® – Novartis

● Fluarix® – GlaxoSmithKline

● Fluvax® – CSL/United Italian Trading (M) Sdn Bhd

● Inflexal V® – Crucell/Propharm

● Influvac® – Abbott

● FluQuadri™ – Sanofi Pasteur*

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
Mode of Administration

- Inactivated influenza virus vaccines have been given by intramuscular, subcutaneous, intradermal, intranasal and oral 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.
- The most frequent adverse effects are local acute inflammatory reactions. Pain, erythema and induration, which are generally mild and rarely interfere with daily activities, occur at the site of vaccine administration in up to 65% of recipients – more commonly with adjuvanted than with unadjuvanted vaccines. Local reactions rarely persist for longer than 24-48 hours.
● The most common systemic reactions include fever, myalgia, arthralgia and headache.

● To date, the most frequently reported adverse events for influenza vaccines received by the National Adverse Drug Reactions Monitoring Centre, NPCB are local site reactions such as injection site pain and swelling, fever, flu-like syndrome, headache, fatigue, muscle pain 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

● Persons aged 50-59 years have been identified as a target group since approximately 1/3 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.

Evidence for Effectiveness

- Meta-analyses generally find that vaccine effectiveness is in the range of 50-80% for older children and healthy adults, but highlight the relative lack of data among other age and risk groups.

- 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 to the Hajj in Saudi Arabia should consider influenza vaccination use.

- Elderly subjects generally respond less effectively to influenza vaccines than young healthy adults. Those with chronic debilitating medical conditions generally do not respond as effectively than 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 old folk homes 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

3. Hui LS, Rashwan H, bin Jaafar MH, Hussaini MH and Isahak DI. Effectiveness of influenza vaccine in preventing influenza-like illness among Faculty of Dentistry staff and students in Universiti Kebangsaan Malaysia. Health Care Infect 2008 ; 13(1) 4–9
Japanese Encephalitis

Introduction

Japanese encephalitis (JE), a mosquito-borne flaviviral infection, is the leading recognised cause of childhood encephalitis in Asia. In economically advanced Asian countries, such as Japan, Korea, Taiwan and Singapore, the integration of JE vaccine into routine immunisation programmes has led to the near elimination of JE. With the near-eradication of poliomyelitis, JE is the continent’s leading cause of childhood viral neurological infection and disability. JE is a major public health problem that is controllable by proven effective vaccines.

The great majority of infections are not apparent and only 1 in approximately 250 infections results in symptomatic illness in susceptible Asians. The principal recognised clinical manifestation of illness is encephalitis. Milder clinical presentations (such as aseptic meningitis, flaccid paralysis and febrile illness with headache) may sometimes occur but usually escape detection. The incubation period is 5-15 days. Illness usually begins with abrupt onset of high fever, change in mental status, gastrointestinal symptoms and headache, followed gradually by disturbances in speech or gait or other motor dysfunction. Irritability, vomiting and diarrhoea or an acute convulsion may be the earliest signs of illness in an infant or child. Seizures occur in more than 75% of pediatric patients and less frequently in adults.

A hospital-based surveillance system for Japanese encephalitis has been in operation in Sarawak, Malaysia since 1997. JE is endemic in Sarawak, with cases occurring throughout the year and a seasonal peak in the last quarter. Out of 133 cases, 92% were children aged 12 years or younger. The introduction of JE vaccination in July 2001 reduced the number of JE cases – 84 in the 4 seasons versus 49 in the 6 seasons following introduction of the vaccine. After implementation of the programme, the mean age of infected children increased from 6.3 to 8.0 years suggesting the need for a catch-up programme.
Vaccines

- Worldwide, 3 types of JE vaccines are in widespread production and use:
  - Inactivated JE vaccine produced in mouse brain.
  - Live attenuated SA 14-14-2 vaccine.
  - Live attenuated JE vaccine grown in primary hamster kidney (PHK) cells.
- Korean Green Cross Japanese Encephalitis Vaccine® is a mouse brain-derived vaccine.
- Imojev® is a live attenuated, monovalent viral vaccine produced using recombinant technology propagated in Vero cells from the SA 14-14-2 strain.
- CD.JEVAX®, a live attenuated JE vaccine prepared by passaging JE virus, strain SA14-14-2, in monolayer of primary hamster kidney cell culture.

Vaccines Available in Malaysia

- Imojev® (Live attenuated recombinant JE vaccine)
  - Sanofi Pasteur*
- Japanese Encephalitis Vaccine® (mouse brain derived JE vaccine)
  - Green Cross Corporation/Propharm
- CD.JEVAX® (Live attenuated JE vaccine)
  - Chengdu Institute of Biological Products/Idaman Pharma

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
Mode of Administration

- In most areas of Asia, the mouse brain derived vaccine produced from the Nakayama strain is given subcutaneously in two 0.5mL doses 1-4 weeks apart (1.0mL for individuals older than 3 years), usually beginning at the age of 12-36 months, with a booster dose at 1 year and additional booster doses thereafter at 1-3 year intervals.

- For Imovex® (live attenuated recombinant JE vaccine), primary vaccination for children at least 9 months of age and older is given as a single dose subcutaneous injection of 0.5mL. A booster dose should be given preferably 1 year after the first vaccination and can be given up to 2 years after the first vaccination. For individuals aged 18 years and above, a single dose is adequate.

- With CD.JEVAX® (live JE vaccine), primary immunisation for persons at least 9 months of age and older is given as a single dose of 0.5mL subcutaneously, and a booster dose can be given from 3 months to 1 year after primary dose. For individuals aged 18 years and above, a single dose is adequate.

- For Japanese Encephalitis Vaccine® (mouse brain-derived JE vaccine), primary vaccination is given as 3 doses of 1mL on days 0, 7 and 28 or 2 doses of 1mL at intervals of 1-4 weeks. Booster dosage of 1mL dose is given every 3 years.

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

- 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.

- Local tenderness, redness, or swelling at the injection site occurs in approximately 20% of persons immunised with inactivated mouse brain-derived vaccines. Mild systemic symptoms (chiefly headache, low-grade fever, myalgias, malaise and gastrointestinal symptoms) are reported by 10-30% of vaccines.

- **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.

- **CD.JEVAX** should not be administered to persons:
  - With a proven or suspected history of hypersensitivity/anaphylactic reaction to any component of the vaccine, including gelatin.
  - With fever, acute infectious disease, tympanitis or active untreated tuberculosis.
  - With malnutrition, general allergy and convulsion.
  - With cardiac, liver or kidney troubles.
  - Undergoing any type of immunosuppressive therapy.
  - With 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 and rash, have been reported after injection but normally do not last longer than 2 days. Most are relieved spontaneously without requiring any particular treatment.

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

Target Groups in Malaysia

- With safe and effective new JE vaccines available, vaccination is recommended for all expatriates whose principal residence is in an area where JE is enzootic.
- Children in Sarawak receive the SA 14-14-2 JE vaccine at 9 and 21 months under the Expanded Programme of Immunisation (EPI).
- Administration of a registered JE vaccine is recommended for selected travelers to Asia and is not yet recommended as a routine immunisation.
- Immunisation is advised for all 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).

Evidence for Effectiveness

- A progressive decline in antibody levels after vaccination with mouse brain-derived vaccines has been observed in the 1st year after primary immunisation with 2 doses. Cross-sectional serosurveys in Japan and Taiwan demonstrate a rapid decline of antibody levels in childhood. Recommendations for booster doses after a 2-dose primary immunisation series in endemic settings are universally made.
- Several clinical trials have demonstrated that 28 days following vaccination with a single dose of Imojev®, protective levels of neutralising antibodies against the homologous vaccine virus strain were present in 96% of vaccine-naïve children aged 12-24 months and 99% of adults. Establishment of immunological memory in vaccinated adult subjects has also been demonstrated.
For CD.JEVAX® vaccine, several studies have demonstrated an excellent immune response after a single dose of SA 14-14-2 vaccine, with neutralising antibody responses produced in 85-100% of non-immune children. Several field trials in China have yielded protective efficacy rates above 95%. One early case control study found 80% vaccine efficacy in children receiving 1 dose and 98% for 2 doses. A more recent study in an endemic area of Nepal reported 99.3% efficacy of a single dose. One year after immunisation, a follow-up study in the same region reported efficacy of 98.5%.

References

Measles

Introduction

Measles is highly infectious. In the pre-vaccination period, >90% of individuals were infected by the age of 10 years, the majority with symptoms. Measles occur only in humans; measles virus is transmitted by aerosolised respiratory droplets and by direct contact. The incubation period is 10-14 days (range 8-15 days) from exposure to onset of rash. Patients are contagious from about 4 days before eruption of the rash until 4 days after eruption.

The most commonly cited complications associated with measles infection are otitis media, pneumonia, diarrhoea, post-infectious encephalitis, subacute sclerosing panencephalitis (SSPE), and death. Complications are likely to be present if the fever has not lysed within 1-2 days of rash onset. The risk of serious complications and death, is increased in children younger than 5 years and adults older than 20 years. Pneumonia, which is responsible for approximately 60% of deaths, is more common in young patients, whereas acute encephalitis occurs more frequently in adults. Pneumonia may occur as a primary viral pneumonia (Hecht pneumonia) or as a bacterial superinfection, most commonly with staphylococcus, pneumococcus or typable (encapsulated) Haemophilus influenzae.

Vaccines

- A number of live attenuated measles vaccines are available, either as monovalent vaccine or as measles-containing vaccine (MCV), in combination with rubella, mumps or varicella vaccines or some combination of these. When using the combined measles-rubella 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.
Vaccines Available in Malaysia

- **M-M-R II®** (Live attenuated measles, mumps and rubella vaccine)
  - Merck Sharp & Dohme

- **Priorix®** (Live attenuated measles, mumps and rubella vaccine)
  - GlaxoSmithKline

- **Measles vaccine®** (Live attenuated measles vaccine)
  - Serum Institute of India/SM Biomed

- **Measles and Rubella®** (Live attenuated measles and rubella vaccine)
  - Serum Institute of India/SM Biomed

Mode of Administration

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

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 vaccine or MMR. Immunogenicity and reactogenicity of the individual components are similar when measles containing vaccines (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, poliovirus vaccines (oral polio vaccine [OPV] or inactivated polio vaccine [IPV]), 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

- Administration of immunoglobulins or other antibody-containing blood products may neutralise the effect of the vaccine for 3-11 months, depending on the dose of measles antibody. Following measles vaccination, recipients of such blood products should be avoided for 2 weeks if possible.

- 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. Theoretically, measles vaccine – alone or in combination with other vaccines – should also be avoided by pregnant women.

- 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 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.

- Allergic reactions to vaccine components, including neomycin and the stabilisers gelatin or sorbitol, may follow 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 Adverse Drug Reactions Monitoring Centre, NPCB are local site reaction such as injection site pain and swelling, fever, nausea and vomiting.
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 – for example, those who are travelling to areas where measles is endemic.

- College and university students: 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 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.

Implications for Healthcare Workers (HCWs)

- The importance of vaccinating health workers is underlined by measles outbreaks occurring in health institutions, affecting both health workers and patients. It is recommended that all healthcare workers without history of measles or measles vaccination should be vaccinated.

Evidence for Effectiveness

- Internationally available measles vaccines are safe, effective and may be used interchangeably within immunisation programmes. Person-to-person transmission of measles vaccine strains has never been documented.

- Following vaccination, the long-term persistence of neutralising measles antibodies is 26-33 years.

References

Mumps

Introduction

Mumps is caused by a paramyxovirus. In approximately 30% of cases, the infection is asymptomatic. Most infections in children aged <2 years are subclinical. People with mumps are contagious from about 2 days before the onset of swelling of the parotid glands up to 9 days after the onset of swelling. Mumps encephalitis is reported in 0.02-0.3% of cases. Although the case-fatality rate of mumps encephalitis is low, permanent sequelae (including paralysis, seizures and cranial nerve palsies) may occur.

Orchitis occurs in 20% 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 for patients. Acquisition of mumps during the first 12 weeks of pregnancy is associated with a 25% incidence of spontaneous abortions, but foetal malformations following infection with mumps virus during pregnancy have not been found.

Pancreatitis is reported as a complication in approximately 4% of cases, but the relationship between mumps pancreatitis and diabetes mellitus remains speculative.

Vaccines

- The vaccine is available in trivalent (measles-mumps-rubella – MMR) or tetravalent (measles-mumps-rubella-varicella) formulations.
Vaccines Available in Malaysia

- **M-M-R II**® (Live attenuated measles, mumps and rubella vaccine)
  - Merck Sharp & Dohme

- **Priorix**® (Live attenuated measles, mumps and rubella vaccine)
  - GlaxoSmithKline

- **Measles, Mumps & Rubella vaccine**® (Live attenuated measles, mumps and rubella vaccine)
  - Serum Institute of India/SM Biomed

Mode of Administration

- All current mumps vaccines are supplied as lyophilised powders and are administered subcutaneously following reconstitution with sterile water.

Co-administration with Other Vaccines

- MMR can be administered simultaneously with diphtheria and tetanus toxoids and acellular or whole-cell pertussis vaccine (DTP/DTaP), with oral or inactivated poliovirus vaccine, with *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. Simultaneous administration of varicella vaccine in combination with separate measles, mumps and rubella vaccines (**Priorix-Tetra**®) or with MMR vaccine, but in separate sites has been shown to be immunogenic. However, a small increased risk of febrile seizures is associated with tetravalent vaccine use vs concomitant administration of MMR and varicella vaccines in children aged 12-23 months receiving the vaccine as the 1st dose.
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 immunoglobulin or deferred until 3 months after such administration because passively acquired antibody can interfere with response to the vaccine.

- 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 fewer 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 Adverse Drug Reactions Monitoring Centre, NPCB are local site reactions such as injection site pain and swelling, fever and rash.

Target Groups in Malaysia

- MMR vaccine is recommended for all children and for certain high-risk groups of adolescents and adults. Certain adults who may be at increased risk for exposure to and transmission of mumps should
receive special consideration for vaccination. These people include international travelers, people attending universities and other higher educational institutions, and people who work at healthcare facilities.

Implications for Healthcare Workers (HCWs)

- Infection control failures resulting in nosocomial transmission have occurred during mumps outbreaks involving hospitals and long term care facilities that housed adolescent and young adult patients. Exposures to mumps in healthcare settings also can result in added economic costs associated with sick leave or reassignment of staff members from patient care duties or closure of wards.

- All persons who work in healthcare facilities should be immune to mumps. Healthcare workers with no history of mumps vaccination and no other evidence of immunity should receive 2 doses (at a minimum interval of 28 days between doses). Healthcare workers who have received only 1 dose previously should receive a 2nd dose.

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

5. Updated Recommendations of the Advisory Committee on Immunisation Practices (ACIP) for the Control and Elimination of Mumps. MMWR June 9, 2006 / 55(22);629-630
Rubella

Introduction

Rubella is a contagious viral disease characterised by fever, rash and swollen glands. The rash, which may be itchy, first appears on the face and progresses from head to foot, lasting about 3 days. As many as half of all rubella cases occur without a rash. Arthralgia and arthritis commonly observed in adults are associated with virus replication or latency in the synovia.

Although most cases are mild, if rubella is contracted early in pregnancy, it can spread from the mother to her developing foetus through the bloodstream and result in birth defects and/or foetal death. Infection in the first 3 months tends to result in serious ocular or cardiac disease, whereas infection late in first half of pregnancy, is more likely to result in isolated deafness.

The goal of rubella vaccination programmes is the prevention of intrauterine infection that causes congenital rubella syndrome (CRS).

Malaysia adopted a selective immunisation programme in 1987 for female school children aged 16 years and supplementary immunisation activities (SIA) for women of child-bearing age in clinics. In 1990, it was given to schoolgirls at age 15 years, and later in 1993, the age was changed to 12 years with catch-up vaccination for the three cohorts who missed their vaccination. In 2002, rubella vaccination was given to all children, with the 1st dose at 12 months and 2nd at 7 years old.

CRS continues to occur because of transmission among unvaccinated children and adults. A study in 2002 revealed that 92.7% of women aged 15-26 years were immune to rubella, 92.9% in the 27-34 age group and only 88.9% in the 35-46 age group. The 15-26 age group represented those women who had rubella immunisation and very high rubella seropositivity (92.7%).
It is noted that although seropositivity of rubella antibodies has improved from 47.9% (pilot study before vaccination programme) to 92.7%, the occurrence of CRS continues. In 2002, the Ministry of Health changed the strategy to replace monovalent measles and rubella vaccines to universal MMR vaccines for all boys and girls at 1 year of age. The Malaysian government continues to give rubella vaccine to older children and women of child-bearing age. In the private hospitals and clinics, rubella antibody screening is done during antenatal visits. Rubella immunisation at postpartum is offered to those found to be susceptible. With this three-pronged attack and surveillance, the elimination of CRS in the near future seems very promising.

Vaccines

- Live attenuated rubella vaccine containing Wistar RA27/3 strain.
- When rubella vaccine is given to children or adults, it is almost always given in combination with measles and mumps vaccines as MMR or MMRV (measles-mumps-rubella-varicella) vaccines.

Vaccines Available in Malaysia

- **Rubella®** (Live attenuated rubella vaccine)  
  – Serums Institute of India/SM Biomed
- **Measles and Rubella®** (Live attenuated measles and rubella vaccine)  
  – Serum Institute of India/SM Biomed
- **Priorix®** (Live attenuated measles, mumps, and rubella vaccine)  
  – GlaxoSmithKline
- **M-M-R II®** (Live attenuated measles, mumps, and rubella vaccine)  
  – Merck Sharp & Dohme
Mode of Administration

- MMR vaccine is administered 0.5mL dose subcutaneously.

Co-administration with Other Vaccines

- Rubella or MMR 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

- **Concurrent IgG:** vaccination within 2 weeks before recipient of IgG or 3 months after recipient of IgG is inadvisable. However, anti-Rh<sub>o</sub>(D) globulin does not interfere with vaccination of postpartum women. Women who are vaccinated after receiving anti-Rh<sub>o</sub>(D) globulin should be tested 6 weeks later for rubella antibodies.

- **Pregnancy:** although there is now abundant evidence for the safety of RA27/3 for the foetus, pregnancy remains a contraindication to rubella vaccination and, women are advised to take precautions against pregnancy for 1 month after vaccination.

- **Common side effects:** vaccinees sometimes develop mild rubella, including rash, lymphadenopathy, fever, sore throat and headache as well as mild local reactions. The incidence varies directly with age, being almost absent in infants but present up to 50% of women.

- To date, the most frequently reported adverse events for rubella vaccines received by the National Adverse Drug Reactions Monitoring Centre, NPCB include fever and rash.
Target Groups in Malaysia

- All adult females especially childbearing age.
- Military recruits and college students.

Implications for Healthcare Workers (HCWs)

- Outbreaks of rubella in hospital with the resultant exposure of pregnant women, have led to the recommendation of compulsory rubella vaccination for both male and female hospital employees.

Evidence for Effectiveness

- Vaccination induces antibodies of IgM, IgG, IgA classes and cellular immunity. Most studies of immunogenicity report 90-100% seroconversion by 21-28 days after vaccination. An outbreak of rubella in France permitted a calculation of effectiveness. Effectiveness of RA 27/3 against clinical rubella was 95% (85-99% CI).

References

2. Epidemiology Unit, Ministry of Health. Executive Summary on Pilot Study of Rubella Vaccination. 1986
Introduction

Meningococcal disease most commonly is 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 basis of 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 UK and US have revealed that students, in the 1st year of college and living in dormitories are at higher risk of meningococcal disease, compared to other college students and age matched general population.

Vaccines

- Meningococcal vaccines are derived from the capsular polysaccharide. Currently tetravalent vaccines protecting against A, C, Y and W135 are available. However, Group B polysaccharide is poorly immunogenic in humans and until recently no vaccines are available for this group. Conjugate vaccines either conjugated to diphtheria toxoid or CRM187 (a non-toxic protein of *Corynebacterium diptheria*) have improved primary response to vaccination and strong anamnestic response at re-exposure.

A vaccine against serogroup B meningococcal disease is used in some countries but it is not currently available in Malaysia.
Vaccines Available in Malaysia

● Quadrivalent (ACWY) conjugate vaccine
  – Menactra® (serogroups A, C, W135 and Y polysaccharides conjugated with diphtheria toxoid protein)
    – Sanofi Pasteur*
  – Menveo® (serogroups A, C, W135 and Y conjugated with non-toxic C. diphtheriae CRM197 protein)
    – Novartis
  – Nimenrix® (serogroups A, C, W135 and Y conjugated tetanus toxoid carrier proteins)
    – GlaxoSmithKline

● Quadrivalent (ACWY) polysaccharide vaccine
  – Menomune® (serogroups A, C, W135 and Y)
    – Sanofi Pasteur*
  – Mencevax ACWY® (serogroups A, C, W135 and Y)
    – GlaxoSmithKline

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
Mode of Administration

- Quadrivalent conjugate vaccines should be administered in preference to the polysaccharide vaccines.
- 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 conjugate vaccine at 5-yearly intervals. For persons who have received a dose of polysaccharide vaccine, a booster dose of conjugate vaccine is recommended 3 years after the last dose of polysaccharide vaccine.
- Persons with other risks 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.

The 2 different conjugate vaccine products can be used interchangeably for the booster doses.

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 Adverse Drug Reactions Monitoring Centre, NPCB include local site reactions such as injection site rash and tenderness, fever, muscle pain and rash.

**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 (depending on the brand administered*), as a condition to enter the country. Accompanying children aged ≤2 years should receive the full course of conjugated meningococcal vaccine (ie Menactra® and Nimenrix®).
- Laboratory staff who frequently handle *N. meningitidis*.
- Travellers 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 on 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.

* The duration of protection is only 2 years for Mencevax® while other vaccines is within 3-5 years.
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. A case control study looking at conjugate vaccine effectiveness in adolescents has shown an overall estimate of vaccine effectiveness of 69%. However, the effectiveness seems to wane with time.

In the case of polysaccharide vaccine, clinical efficacies of >85% have been demonstrated among school children and adults during serogroup A and C outbreaks. Serological studies show reduced antibody response after repeated doses (immunologic hyporesponsiveness).

References

2. Bruce MG, Rosenstein NE, Capparella JM, Shutt KA, Perkins BA, Collins M. Risk factors for meningococcal disease in college students. JAMA. 2001;286(6):688-93
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. 91 serotypes have been identified based on antigenic differences in their capsular polysaccharides. Type-specific antibody to this capsular polysaccharide is protective. Vaccination is recommended for the prevention of invasive pneumococcal disease (IPD) which includes bacteraemia, meningitis, or infection of other normally sterile sites.

Vaccines

- There are 2 different types of pneumococcal vaccines – pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPV). PCV is immunogenic in young infants and can induce an immune memory response. PPV is poorly immunogenic in children <2 years and does not induce immune memory. However PPV covers more serotypes.

  - **Pneumococcal conjugate vaccine (PCV)**
    
    The first pneumococcal conjugate vaccine (PCV7) was registered in Malaysia in 2002. It includes purified capsular polysaccharide of 7 serotypes of *S. pneumoniae* (4, 9V, 14, 19F, 23F, 18C, and 6B) conjugated to a non-toxic variant of diphtheria toxin known as CRM197. In 2009, a 10 valent pneumococcal conjugate vaccine (PCV10), was registered in Malaysia. It had serotypes 1, 5, 6B, 7F, 9V, 14, 23F and 4, conjugated to a non-typeable *H. influenzae* protein D, serotype 18C conjugated to tetanus toxoid carrier protein and serotype 19F, conjugated to diphtheria toxoid carrier protein.
In 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) was registered. It contains the 7 serotypes of S. pneumoniae as PCV7 plus serotypes 1, 3, 5, 6A, 7F and 19A, which are also conjugated to CRM197.

— Pneumococcal polysaccharide vaccine (PPV)
  • It contains pneumococcal capsular polysaccharide of serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F.

— 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%).

Vaccines Available in Malaysia

● Polysaccharide vaccine (PPV)
  — Pneumo 23 Polyvalent Vaccine – Sanofi Pasteur*
  — Pneumovax 23 Vaccine® – Merck Sharp & Dohme

● Conjugate vaccine (PCV)
  — Prevenar 13® (PCV13) – Pfizer

*Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
Target Groups in Malaysia

- **Category A: conditions associated with the highest increased risk of IPD**
  - Functional or anatomical asplenia including:
    - Sickle cell disease or other haemoglobinopathies.
    - Congenital or acquired asplenia (splenectomy), splenic dysfunction.
  - Immunocompromised conditions including:
    - Congenital or acquired immune deficiency, including B-(humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).
    - Immunosuppressive therapy (including individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone 20mg or more per day) or radiation therapy, where there is sufficient immune reconstitution for vaccine response to be expected.
    - Haematological and other malignancies.
    - Solid organ transplant.
    - Haemopoietic stem cell transplant (HSCT).
    - HIV infection (including AIDS).
    - Chronic renal failure, or relapsing or persistent nephrotic syndrome.
    - Proven or presumptive cerebrospinal fluid (CSF) leak.
    - Cochlear implants.
    - Intracranial shunts.
● **Category B: conditions associated with an increased risk of IPD**
  
  — Chronic cardiac disease, including congestive heart failure, congenital heart disease and cardiomyopathies (excluding hypertension only).
  
  — Chronic lung disease, including chronic obstructive pulmonary disease, emphysema, and asthma (requiring frequent hospital visits and use of multiple medications).
  
  — Diabetes mellitus.
  
  — Downs syndrome.
  
  — Alcoholism.
  
  — Chronic liver disease including cirrhosis, biliary atresia, chronic hepatitis.
  
  — Tobacco smoking.

● Persons age > 60 years

● Persons going for religious pilgrimages (eg Hajj)

**Mode of Administration**

● **Category A conditions:**
  
  — *Pneumococcal vaccine-naïve persons:*
    
    Those with highest increased risk of invasive pneumococcal disease should receive a dose of PCV13 first, followed by a dose of PPV23 6-12 months later. A 2nd dose of PPV23 is recommended for all at-risk adults in Category A, approximately 5-10 years (minimum of 5 years), after the 1st dose of PPV23. A 3rd dose of PPV23, is recommended at 60 years of age or a minimum of 5 years after the 2nd dose, whichever is later.
— **Previous vaccination with PPV23:**

- Those with highest increased risk of invasive pneumococcal disease and who have already received 1 or more prior doses of PPV23, should receive 1 dose of PCV13 at least 12 months after the most recent dose of PPV23. A 2nd dose of PPV23 is recommended approximately 5-10 years (minimum of 5 years) after the 1st dose of PPV23. A 3rd dose of PPV23 is recommended at age 60 years or a minimum of 5 years after the 2nd dose, whichever is later.

- No more than 3 doses of PPV23 are recommended during a person’s adult life.

- **Category B conditions:**
  - For adults who have a condition listed in Category B, it is recommended to give 1 dose of PCV13.

- **Age 60 years and above:**
  - A single dose of PCV13 is recommended.

- **Persons going for religious pilgrimages:**
  - Adults should receive a single dose of PCV13 or PPV23. Accompanying children aged ≤2 years should receive the full course of PCV.
Contraindications and Adverse Effects

- 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 newborn 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 Adverse Drug Reactions Monitoring Centre, NPCB 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.
● In Malawi, a study of adults, most of whom were HIV-infected, showed that 2 doses of PCV7 administered 4 weeks apart had a vaccine efficacy of 74% against IPD. However, there are currently no data on clinical outcomes for PCV13.

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

References

**Introduction**

Poliomyelitis is an acute communicable disease caused by poliovirus serotypes (1, 2 and 3). It is spread mainly by the faecal-oral route. Before polio vaccination became a public health policy, almost all children were infected with poliovirus. On average, about 1 in 75 adults who are infected, will develop paralytic poliomyelitis. The last case of wild type poliomyelitis in Malaysia was reported in 1990. In 2000, WHO certified Malaysia as polio-free. However, vigilance is still needed.

In May 2014, WHO has declared that polio is a public health emergency of international concern as 3 countries are still endemic with wild poliovirus and 4 countries are exporting this virus to other countries. Hence the risk for re-introduction of infection is still high with movement of people from country to country.

**Vaccines**

- Inactivated poliomyelitis vaccine (Salk), was introduced in 1956 for routine vaccination and was replaced by live attenuated oral vaccine (Sabin) in 1962. 2 types of poliovirus vaccines are currently available: oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV). A primary vaccination series with either vaccine, produces immunity to all 3 serotypes of poliovirus in more than 95% of recipients.

**Vaccines Available in Malaysia**

- **Opvero** (Live attenuated polio-oral)*
  – Sanofi Pasteur*

- **Oral poliomyelitis vaccine** (Live attenuated polio-oral)
  – Bio Farma/Propharm

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
* Registered in Malaysia but not marketed. For products that are registered in Malaysia but not marketed or commercially available, General Practitioners can make a request through the vaccine company representatives and the information will be cascaded to the Product Manager. The Product Manager can then liaise with supply chain to help bring in the requested stock but this will depend on the availability.
● **Polio Sabin (Oral) Vaccine®** (Live attenuated polio-oral)
  – GlaxoSmithKline

● **Poliorix solution for injection®** (Inactivated polio vaccine)†
  – GlaxoSmithKline

● **Imovax Polio** (Inactivated polio vaccine)#
  – Sanofi Pasteur*

Note: IPV is also available in combination with DTP but dosage is available only for children less than 7 years old.

**Mode of Administration**

● **Oral polio vaccine (OPV)**
  – Primary vaccination comprises 3 doses; the 1st 2 doses are given 6-8 weeks apart and the 3rd dose is given 6 weeks to 12 months after the 2nd dose.

● **Inactivated poliovirus vaccine (IPV)**
  – Primary vaccination comprises 3 doses; the 1st 2 doses are given 4-8 weeks apart and the 3rd dose is given 8-12 months after the 2nd dose.
  – Given intramuscularly over the deltoid region.

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
* Registered in Malaysia but not marketed. For products that are registered in Malaysia but not marketed or commercially available, General Practitioners can make a request through the vaccine company representatives and the information will be cascaded to the Product Manager. The Product Manager can then liaise with supply chain to help bring in the requested stock but this will depend on the availability
† Registered in Malaysia but not marketed
Target Groups in Malaysia

- Travellers to polio-endemic countries or polio-affected areas, who have previously received ≥3 doses of OPV or IPV, should be offered another dose of polio vaccine as a once-only dose before departure.
- Travellers from endemic countries to a non-endemic country should similarly receive 1 dose of OPV or IPV.

Implications for Healthcare Workers (HCWs)

- Healthcare workers, including laboratory personnel, who are likely to be in contact with cases or poliovirus should be given booster doses every 10 years.

Contraindications and Adverse Effects

- OPV should not be given to persons and household contacts of the immunocompromised. OPV should be given either 3 weeks before or 3 months after an injection of immunoglobulin.
- In general, vaccination of pregnant women and immunocompromised persons should be avoided. However, if immediate protection is needed eIPV is recommended.
- OPV has, in rare instances, been associated with paralysis among healthy recipients and their contacts. The risk however is very low. No serious side effects have been documented with eIPV but as the vaccine contains trace amounts of streptomycin and neomycin, hypersensitivity to these antibiotics may occur.
- To date, the most frequently reported adverse event for OPV received by the National Adverse Drug Reactions Monitoring Centre, NPCB is fever. Cases of febrile seizure and convulsions had also been reported in children.
References

Introduction

Malaysia has been declared rabies-free from the year 1997. However, there is still a risk of getting infected from animals that are imported or smuggled in without the necessary approval. The last reported case of dogs having rabies was in Terengganu from November 1995 to June 1996, when 6 rabid dogs bit 9 people. Fortunately, none of the victims contracted rabies.

Generally, the risk of contracting rabies from animal bites in Malaysia is low. However, there are certain situations where a higher risk of contracting rabies may be encountered:

- Animal bites occurring in areas bordering Thailand and Indonesia.
- Travellers who had been bitten by animals in rabies endemic areas.

Vaccines

- Rabies vaccine is a killed vaccine which may be derived from cell culture or embryonated eggs. Cell culture vaccines (CCVs) includes human diploid cell lines (HDCV), purified vero cell-based vaccine (PVRV) and purified chick embryo cell vaccine (PCECV). Rabies vaccine is effective when used for pre-exposure and post-exposure prophylaxis.
- Human rabies immunoglobulin is also used for post exposure prophylaxis (see section on Passive Immunisation, pg 144).
Vaccines Available in Malaysia

- **Verorab** (PVRV – Purified inactivated rabies vaccine, prepared on vero cells) – Sanofi Pasteur*
- **Merieux** (HDCV – Inactivated rabies vaccine, prepared on human diploid cell) – Sanofi Pasteur*

Immunoglobulin

- **HRIG** (Human rabies immunoglobulin)*^ – Sanofi Pasteur*

Target Groups in Malaysia

- **Pre-exposure vaccination is advisable for:**
  - People with high exposure to rabies such as laboratory staff working with rabies virus, veterinarians, animal handlers and wildlife officers.
  - People travelling to countries and areas with risk of getting bitten by stray dogs or other rabid animals.

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd


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
IM injections
► In the deltoid muscle in adults and children
► In anterolateral part of the thigh in infants and toddlers

* D28 injection may also be given at D21

- Post-exposure prophylaxis:
  - Post-exposure prophylaxis depends on the type of contact with the confirmed or suspected rabid animal (Refer to Table 14.1).
<table>
<thead>
<tr>
<th>Category</th>
<th>Type of contact with a suspected or confirmed rabid domestic or wild animal or animal unavailable for testing</th>
<th>Type of exposure</th>
<th>Recommended post-exposure prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Touching or feeding of animals Licks on intact skin</td>
<td>None</td>
<td>None if reliable case history is available</td>
</tr>
<tr>
<td>II</td>
<td>Nibbling of uncovered skin Minor scratches or abrasions without bleeding</td>
<td>Minor</td>
<td>Administer vaccine immediately&lt;sup&gt;b&lt;/sup&gt; Stop treatment if animal remains healthy throughout an observation period of 10 days&lt;sup&gt;c&lt;/sup&gt; or is proved to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques</td>
</tr>
<tr>
<td>III</td>
<td>Single or multiple transdermal bites or scratches, licks on broken skin Contamination or mucous membrane with saliva (licks) Exposure to bats&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Severe</td>
<td>Administer rabies immunoglobulin and vaccine immediately Stop treatment if animal remains healthy throughout an observation period of 10 days&lt;sup&gt;c&lt;/sup&gt; or is proved to be negative for rabies by a reliable laboratory, using appropriate diagnostic techniques</td>
</tr>
</tbody>
</table>

<sup>a</sup> Wild animal defined as any animal other than a domestic animal. <sup>b</sup> If vaccine was given within 7 days after bite exposure and the animal remains healthy throughout an observation period of 10 days.<sup>c</sup> Observation period of 10 days begins on day 1 after the bite exposure. <sup>d</sup> Bat exposures may be associated with significant human fatalities when not treated.
a Exposure to rodents, rabbits and hares seldom, if ever, requires specific anti-rabies post-exposure prophylaxis.

b If an apparently healthy dog or cat in or from a low-risk country or area is placed under observation, the situation may warrant delaying initiation of treatment.

c This observation period applies only to dogs and cats. Except in the case of threatened or endangered species, other domestic and wild animals suspected to be rabid should be humanely killed and their tissues examine for the presence of rabies antigen using appropriate laboratory techniques.

d Post-exposure prophylaxis should be considered for individuals who have been in close contact with bats, particularly following bites or scratches or exposure to mucous membrane.

● **Wound treatment**
  — Thorough washing of the wound with soap/detergent and water, followed by application of ethanol or an aqueous solution of iodine or povidone.

● **Passive immunisation**
  — Human rabies immunoglobulin (HRIG) should be used for category III exposures as well as for some category II exposures (see table, above). Passive immunisation should be administered just before or shortly after administration of the 1st dose of vaccine given in the post-exposure prophylaxis regimen. If it is not immediately available, passive immunisation can be administered up until the 7th day after initiation of the primary series of post-exposure prophylaxis (with cell-culture or embryonated-egg rabies vaccine).
Mode of Administration

- Rabies vaccine is a lyophilised vaccine that needs to be reconstituted to 1.0mL before given intramuscularly.

  - **Pre-exposure prophylaxis**
    - Intramuscular injection: Three 1.0mL injections of CCVs on days 0, 7 and 28 (day 28 preferable, but administration may be advanced towards day 21 if time is limited).
    - Booster for those at continued risk every 2 years.

  - **Post-exposure prophylaxis with CCVs**
    - Patients who have not been previously vaccinated should receive:
      - 4 doses of rabies vaccine on days 0, 3, 7, and 14
      - **AND**
      - 20IU/kg dose of HRIG.
    - Previously vaccinated patients (those who have previously received post-exposure prophylaxis or have received a 3-dose pre-exposure regimen of CCVs) should be given 2 doses of rabies vaccine on days 0 and 3. HRIG need not be given.

  - **Post-exposure treatment with HRIG**
    - This should be given at the beginning of the post-exposure prophylaxis but, it can be delayed up to the 8th day after the 1st dose of the rabies vaccine.
    - A single 20IU/kg dose is required. Half should be infiltrated into the area of the wound after thorough cleansing by scrubbing with soap and water under a running tap for 5 minutes. The rest is to be administrated intramuscularly, but never in the same site or in the same syringe as the rabies vaccine.
Contraindications and Adverse Effects

- Rabies immunisation is contraindicated in patients who are on immunosuppressive agents including steroids and those with a previous history of anaphylaxis to rabies vaccine. It should be only given to pregnant women if the risk of exposure is high.

- Local adverse effects include pain, erythema and itching at the site of injection. Systemic reactions are mild (fever, headache, nausea, vomiting, abdominal pain, muscle aches and dizziness). Allergic reaction occurs in 11 of 10,000 vaccinees and range from hives to anaphylaxis. Reactions with HRIG include local pain and low grade fever may follow the injection. No serious adverse reactions have been reported.

- To date, the National Adverse Drug Reactions Monitoring Centre, NPCB has not received any AEFI report for rabies vaccines.

Evidence for Effectiveness

- Studies demonstrate remarkably good immunogenicity in both pre-exposure and post-exposure prophylaxis using CCVs. The use of human rabies immunoglobulin (HRIG) in conjunction with vaccination has clearly reduced human rabies mortality.
References

Introduction

Typhoid fever 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 1 of 5 food and waterborne diseases besides cholera, food poisoning, hepatitis A and dysentery which are monitored through the notification system under the Prevention and Control of Infectious Diseases Act 1988 (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 reservoir in endemic areas and are of considerable public health importance, particularly if they work in the food industry.

Typhoid is an endemic in Malaysia however the incidence has shown a declining trend in the past 13 years with an average incidence less than 5 cases per 100,000 population (2000-2013). The incidence rate was 0.73 per 100,000 population in 2013.

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

- There are 2 types of typhoid vaccines which are available in oral or parenteral formulation.
  - 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.
  - The parenteral vaccine contains the S. Typhi Vi polysaccharide which has been inactivated with formaldehyde and extracted from the supernatant.

Vaccines Available in Malaysia

- **Typhim Vi** (Purified Vi capsular polysaccharide vaccine)
  - Sanofi Pasteur*

- **Vivaxim** (Inactivated hepatitis A virus and typhoid Vi capsular polysaccharide)
  - Sanofi Pasteur*

- **Vivotif Oral®** (Oral live attenuated typhoid vaccine)
  - CSL/Propharm

- **Typherix®** (Purified Vi capsular polysaccharide vaccine)
  - GlaxoSmithKline

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
Mode of Administration

- **Oral live attenuated vaccine**
  - It is available in a pack of 3 capsules. The vaccine schedule is as follows: 1 capsule on days 1, 3 and 5 to be taken 1 hour before meals. The capsule must be swallowed whole with water and not chewed.

- **Parenteral Vi polysaccharide vaccine**
  - The monovalent typhoid vaccine is given as a single dose of 0.5mL via IM injection.
  - To maintain immunity, booster doses of the oral vaccine are required every 3 years (**Vivotif®**), and booster doses of the parenteral vaccine are required every 3 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, NPCB are headache and urticaria.

Target Groups in Malaysia

- Food handlers and vendors.
- Travellers to areas in which there is a recognised risk of exposure to S. Typhi.
- Risk is greatest for travellers to developing countries where food hygiene may be suboptimal and drinking water may not be adequately treated. Travellers 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.
- Microbiology laboratory personnel and others who work with S. Typhi.
Implications for Healthcare Workers (HCWs)

- Cases of laboratory-acquired typhoid fever have been reported among persons working in microbiology laboratories. Thus, it is recommended that laboratory personnel and others who work frequently with S. Typhi should be vaccinated with either the oral or parenteral typhoid vaccine. Booster vaccinations should be administered on schedule according to the manufacturer’s recommendations.

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. 2 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

Introduction

The varicella-zoster virus (VZV) causes 2 diseases, varicella (chickenpox) and herpes zoster (HZ, shingles). Infection with VZV (varicella) in temperate climates where vaccination is not used approaches 100% by the 4th decade of life. Whereas varicella may be mild in some people, epidemiologic studies indicate that there is significant morbidity and some mortality with primary infection 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. Varicella vaccine was registered for routine use in childhood in the United States in 1995. Monovalent varicella vaccines are registered and 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 were registered in the United States in 2005.

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

Patients with varicella typically have a generalised vesicular rash concentrated on the head and trunk and fever. In an immunocompetent person, malaise and fever may occur 1 or 2 days before rash onset, but more commonly these symptoms occur concurrently with the appearance of the rash. The rash appears in crops; each crop usually progresses within less than 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 scar.
Varicella in otherwise healthy children is usually not severe, but the disease has a wide variety of infrequent extracutaneous manifestations or complications. These include pneumonia, encephalitis, cerebellar ataxia, arthritis, appendicitis, hepatitis, glomerulonephritis, pericarditis and orchitis. The most common complication in children is secondary bacterial infection. Staphylococci or group A beta-haemolytic streptococci are the usual causative pathogens. Group A streptococcal infections may be unusually severe and even fatal after varicella. Acute cerebellar ataxia may develop before rash onset or up to 10 days afterward, with truncal ataxia often the only neurologic sign. Cerebellar ataxia occurs in about 1 in 4,000 varicella cases among children less than 15 years; the prognosis is usually good. Varicella encephalitis is a more serious and much less common complication (1 in 100,000 cases) than cerebellar ataxia and carries a more guarded prognosis. Adults with varicella have significantly higher case morbidity and mortality with primary VZV infection than children.

In adults, the height and duration of the febrile response are greater and rash is frequently more severe, with a greater number of lesions and increased time for clearing. Constitutional signs and symptoms and a prodrome are of greater intensity in adults.

Varicella may be more severe in pregnant women (especially in the last trimester) than in other adults. Foetal morbidity is increased in pregnant women with 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 infant. Maternal antibodies to VZV may not have formed or crossed the placenta and VZV may infect the baby before or after delivery. In addition, because of the immaturity of the infant’s cellular immunity, it is at risk for severe varicella especially if there is no maternal antibody to VZV. 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

- **Varilrix®** (Live attenuated Oka strain of varicella-zoster virus) – GlaxoSmithKline
- **Varivax®** (Live attenuated Oka/Merck strain of varicella-zoster virus) – Merck Sharp & Dohme
- **Priorix-Tetra®** (Live attenuated measles virus [Schwarz strain], mumps virus [RIT 4385 strain, derived from the Jeryl Lynn strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka strain]) – GlaxoSmithKline
- **ProQuad®** (Live attenuated measles virus [Enders’ attenuated Edmonston strain], mumps virus [Jeryl Lynn B level strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka/Merck strain]); lyophilised powder (contains porcine gelatin) in a monodose vial with a pre-filled diluent syringe) – CSL Limited/Merck & Co Inc
Vaccines Available in Malaysia

- **Varilrix®** (Live attenuated Oka strain of varicella-zoster virus)  
  – GlaxoSmithKline

- **Varivax®** (Live attenuated Oka/Merck strain of varicella-zoster virus)  
  – Merck Sharp & Dohme

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 not approved for use in this age group.**

Contraindications and Adverse Effects

- Although no infants with congenital varicella syndrome secondary to vaccine type virus have been reported, vaccination in pregnancy is contraindicated. The most common adverse effects of monovalent varicella vaccine, accounting for 67% of all reports, have consistently been rash, fever, and injection site reactions.

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

- Varicella-like rashes occuring >2 weeks after vaccination have been reported based on post-marketing data.
Target Groups in Malaysia

- Adults who have no history of previous chickenpox 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 not approved for use in this age group.**

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 travellers, and healthcare workers.

Because a foetus may be affected if a pregnant woman acquires varicella, women who do not have previous natural infection or vaccination are advised to receive varicella vaccination before they start a family. If already pregnant, they should be vaccinated post-natally.

Implications for Healthcare Workers (HCWs)

- Nosocomial transmission of VZV is a well-recognised medical and public health 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. These include selected HIV-infected persons and certain groups of immunocompromised persons.
Evidence for Effectiveness

- A review of 17 post-licensure vaccine effectiveness evaluations in the US in 2008 showed that 1 dose of varicella vaccine (Varivax®) was 84.5% (median; range, 44-100%) effective in preventing varicella and 100% effective (mean and median) in preventing severe varicella. Connecticut case-controlled study through 2010 demonstrated that 2 doses of vaccine provided better protection than 1 dose; vaccine effectiveness for prevention of PCR-confirmed varicella was 98% after 2 doses, compared with 86% for 1 dose (P < .001).

- Studies of United States adults vaccinated in the NIAID collaborative study indicated that 60-90% are seropositive by FAMA or latex agglutination antibody tests as long as 13 years after vaccination. In subsequent follow-up studies of a subset of these vaccinees (120 healthcare workers), 31% lost detectable FAMA antibodies after, on average, 8 years. 12 (10%) developed varicella; all had mild infections despite loss of detectable VZV antibodies. In another analysis of this study, 9% of almost 500 adult vaccinees developed chickenpox, with follow-up for some persons as long as 21 years.

References

Introduction

Yellow fever (YF) is an acute viral haemorrhagic disease. The virus is of the Flavivirus genus. The yellow fever virus is transmitted by the bite of female mosquitoes (several species of the *Haemogogus* and *Aedes* including *Aedes aegypti*) and is found in tropical and subtropical areas in South America and Africa, but not in Asia. Primates and several species of mosquito are the only hosts. The incubation period is 2-5 days. The acute form of the disease is viral haemorrhagic fever which can lead to death within 10 days in 50% of cases in non-indigenous individuals (namely travellers) and during epidemic. Among the indigenous populations in endemic areas fatality is around 5%.

There are 3 reasons for YF vaccination:

- Provides individual protection and reduces the risks of infection for those living in epidemic and endemic YF areas.
- Protects travellers from the endemic or areas with risk of YF infection.
- Prevents the spread of YF by viraemic travellers on an international scale.

Vaccines

- Yellow fever vaccine is a live attenuated freeze dried preparation of the 17D strain of yellow fever virus. A single dose correctly given confers immunity in nearly 100% of recipients.

Vaccines Available in Malaysia

- *Stamaril* (live attenuated yellow fever virus vaccine) – Sanofi Pasteur*

Certification of vaccination can be obtained from the Virology Division, Infectious Diseases Research Centre, Institute for Medical Research Kuala Lumpur and various other designated centres in the country (details can be obtained from the Ministry of Health website – www.moh.gov.my)

* Sanofi Pasteur c/o Sanofi-Aventis (Malaysia) Sdn Bhd
Mode of Administration

- The vaccine should be given by subcutaneous injection as a single 0.5mL dose irrespective of age. The International Certificate is valid for 10 years from the 10th day after primary vaccination and immediately after revaccination.

Contraindications and Adverse Effects

- The vaccine is contraindicated in:
  - Immunocompromised patients.
  - Individuals allergic to eggs.
  - Children before 6 months of age.
  - Patients with symptomatic HIV infection.
  - Pregnant mothers.

- The adverse effects include local site reactions and systemic reactions such as headache, nausea, vomiting, diarrhoea, myalgia and pyrexia. Severe reactions such as vaccine-associated viscerotropic diseases have been rarely reported.

- To date, the reported adverse events for YF vaccines received by the National Adverse Drug Reactions Monitoring Centre, NPCB include shortness of breath, cough, numbness, body aches, anaemia and allergic reaction.

Target Groups in Malaysia

- Persons travelling or living in areas in which yellow fever infections occur. Vaccination is mandatory for all persons travelling from or to countries endemic for yellow fever (refer to the WHO website for the current list of countries www.who.int/ith).

- Laboratory personnel who may be exposed to the virulent virus.
Evidence for Effectiveness

- Close to 100% seroconversion rates have been shown with yellow fever 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.

References

**Introduction**

The clinical course of acute zoster is variable. It is usually less severe in children and younger adults. Typically, zoster begins with a prodrome. Headache, photophobia and malaise might occur, with fever being less common. Abnormal skin sensations and pain of varying severity are the most common symptoms. These symptoms can precede the zoster rash by days to weeks and rarely might be the only clinical manifestation of VZV reactivation. Pain is described as aching, burning, stabbing, or shock-like. Altered sensitivity to touch, pain provoked by trivial stimuli, and unbearable itching are all frequently reported.

A common and potentially debilitating consequence of zoster is post herpetic neuralgia (PHN), a persistent pain after resolution of the rash. The pain of PHN can last for weeks or months and occasionally persists for many years. In addition to PHN, zoster is associated with a variety of other complications. Among persons with zoster, 10-25% have herpes zoster ophthalmicus (HZO).

In immunocompromised persons, zoster initially might present typically. However, the rash tends to be more severe and its duration prolonged. One specific risk for persons with some immunocompromised conditions is dissemination of the zoster rash.

**Vaccines**

- The zoster vaccine contains the Oka strain of VZV developed for the varicella vaccine. It is produced by Merck & Co, and marketed as **Zostavax®**. This vaccine has a much higher viral concentration and is 14 times more potent than the varicella vaccine. Doctors should note that the vaccine contains porcine gelatin.

**Vaccines Available in Malaysia**

- **Zostavax®** (Live attenuated varicella-zoster virus vaccine)
  – Merck Sharp & Dohme
Mode of Administration

- The vaccine is administered as a single subcutaneous dose. **Zostavax®** should be stored refrigerated at an average temperature of 2-8°C or colder until it is reconstituted for injection. The diluent should be stored separately at room temperature (20-25°C) or in the refrigerator (2-8°C) before reconstitution, protect from light.

**Discard if reconstituted vaccine is not used within 30 minutes. Do NOT freeze reconstituted vaccine.**

Co-administration with Other Vaccines

- In general, the simultaneous administration of widely used live attenuated and inactivated vaccines has not resulted in an increase in adverse events or a reduction in immunogenicity of the vaccines.

Contraindications and Adverse Effects

- Zoster vaccine should not be given to:
  - Persons who have no previous varicella infection (varicella vaccine should be given instead).
  - Persons who have had previous varicella vaccination.
  - Immunocompromised persons.
  - Persons with active tuberculosis.
  - Persons with a history of anaphylactic/anaphylactoid reactions to any of the vaccine components.
  - Persons who are receiving or have recently received (eg 48 hours) anti-viral drugs active against herpesviruses because these drugs may interfere with the protective effect of zoster vaccine. These drugs should be avoided for 10 days after zoster vaccine administration.
● The adverse effects include local site reactions and systemic reactions such as headache, pruritus, haematoma, warmth, induration and pain in extremity.

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

Target Groups in Malaysia

● Zoster vaccine is recommended for persons who are 60 years and above, provided there are no contraindications (see above). 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 60 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

● The vaccine efficacy against HZ was found to be between 51.3-55.0%.

References

Passive Immunisation

Introduction

Passive immunisation means the administration of a product containing antibodies (or immunoglobulins, IgG) pooled from blood donors in order to provide temporary protection under the following conditions:

- In an unimmunised person exposed to an infection.
- In 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.

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

- Normal (nonspecific) human immunoglobulin – from unselected donors.
- 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 and 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 of contact 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.
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.

**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 the 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.

**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.

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:

- Non-immune pregnant women.
- 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.
Specific Immunoglobulins

Specific immunoglobulins preparation is obtained from a pooled sera of people with antibody to the specific infectious agents. Antisera from animals, usually horses that are hyperimmunised against a specific organism, are used when human products are not available.

Specific immunoglobulins which are available include:

- **Botulinum antitoxin** (available only in Hospital Kuala Lumpur).
- **Diphtheria antitoxin**: Although not registered in Malaysia, the antitoxin is available in 10 major hospitals based on zones (please see page 34 for the list of hospitals) this is administered before bacteriologic confirmation when there is a clinical suspicion of the disease. It is not recommended for prophylaxis use in close, unimmunised contacts of diphtheria cases.
- **Hepatitis B immunoglobulin**: HB Ig provides effective immediate short term immunity. It should be administered within 48 hours of exposure concurrently with the vaccine (but no later than 7 days after exposure).
  - Indications of its use:
    - Percutaneous or mucosal exposure to blood containing hepatitis B.
    - Sexual contact with an acute case of hepatitis B.
    - Birth of an infant to a mother with acute or chronic hepatitis B infection. It has to be administered within 12 hours of birth and given with the 1st dose of hepatitis B vaccine.
- **Rabies immunoglobulin**: (Not available in Malaysia) Refer to the Section on Rabies for indications for use of the immunoglobulin. It may be necessary to send the patient to Tan Tock Seng Hospital in Singapore (+65 62566011) if the need for immunisation is urgently required.
- **Tetanus immunoglobulin (Tlg)**: Tetanus is a medical emergency and requires immediate treatment with human tetanus immunoglobulin, an anti-tetanus toxoid booster, agents to control the muscle spasm, aggressive wound care and antibiotics. (refer to the section on Tetanus pg 39).
- **Varicella-zoster immunoglobulin (VZlg)**: Although the product is not registered in Malaysia, the product can be made available^\(1\). The decision to administer VZlg to a person exposed to varicella should be based on:
  - Whether the patient is susceptible.
  - Whether the exposure is likely to result in infection.
— Whether the person is at greater risk for complications than in general population.

Persons who at greater risk for severe complications who are not candidates for varicella vaccination who may 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.

VZIg should be administered as soon as possible after exposure but may also be effective if given up to 96 hours after exposure.


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

References
4. Updated Hepatitis A Postexposure Propylaxis and Travellers Vaccination Recommendations. MMWR 2007;56(41):1080-4
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 hemorrhagic fever (DHF) and dengue shock syndrome. DENV is endemic in South and Central America, Southeast Asia and Sub-Saharan Africa. It is estimated that there are more than 50,000,000 dengue infections each year and almost half the world’s population live in countries in which dengue is endemic. 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 and several candidate vaccines are in various stages of development, with promising indications that a safe vaccine is feasible. Vaccination would be a part of an integrated approach in the fight against dengue, with strategies including vector control and environmental management.

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). One of the challenges to the development of a dengue vaccine is that it must induce immunity to all 4 serotypes because of the potential immunopathology of severe dengue seen in subsequent infections by heterologous serotypes, due to antibody dependent enhancement theory.

Vaccines

- Currently no vaccine is registered.

There are a number of candidate dengue vaccines in development including recombinant, live attenuated, inactivated, DNA and viral-vector vaccines, with several undergoing clinical evaluation, (refer to Table 20.1). The lead candidate vaccine by Sanofi Pasteur (CYD dengue vaccine) has recently completed Phase III clinical trials and estimated to be available in the near future. It is a tetravalent, live, attenuated, recombinant chimeric vaccine based on the yellow fever 17D vaccine.
## Table 20.1.
### Tetravalent Vaccine Candidates Under Clinical Development³,⁴.

<table>
<thead>
<tr>
<th>Vaccine Candidates</th>
<th>Vaccine approach</th>
<th>Developer/commercial partner</th>
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<td>CYD-TDV</td>
<td>Chimeric viruses based on YF 17D back bone</td>
<td>Sanofi Pasteur</td>
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<td>LAV</td>
<td>Classically live attenuated viruses derived by passage in primary dog kidney cells</td>
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<td>TV vaccine formulations</td>
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<td>DENVax</td>
<td>Chimeric viruses based on DENV2 PDK 53 background</td>
<td>Inviragen (part of Takeda since May 2013)</td>
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<tr>
<td>DEN-80E</td>
<td>Recombinant subunit envelope proteins produced in insect cells</td>
<td>Hawaii Biotech/Merck</td>
</tr>
<tr>
<td>DPIV</td>
<td>Inactivated vaccine adjuvanted with aluminium or GSK proprietary adjuvant systems</td>
<td>GSK/WRAIR/Fiocruz</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- YF 17D: Yellow Fever 17D vaccine virus strain.
- LAV: Live attenuated virus (classically attenuated vaccine strains).
- WRAIR/GSK: Walter Reed Army Institute of Research/GlaxoSmithKline.
- TV Vaccine formulations: Tetravalent vaccine formulations.
- NIAID LID: National Institute of Allergy and Infectious Diseases, Laboratory of Infectious Diseases.
- DENVax: Trade name of chimeric vaccine approach being evaluated by Inviragen.
- DENV2 PDK53: Dengue virus type 2 strain passaged 53 times in primary dog kidney cells.
- DEN-80E: Recombinant subunit corresponding to the carboxy-terminal approximately 80% of the complete dengue envelope protein.
- D1ME-VR-P: DNA construct under evaluation by the Naval Medical Research Center that includes full-length membrane and envelope genes.
- prM-E: Pre-membrane and envelope.
Vaccines Available in Malaysia

- There are no dengue vaccines available currently.

However a Phase III trial to assess the efficacy and safety of dengue vaccine (CYD14) for healthy children aged 2-14 years has been completed. This is a part of an international multicentre trial involving 10,275 subjects in 5 countries in Southeast Asia including Malaysia, Thailand, Vietnam, Philippines and Indonesia, over a 4-year period from May 2011 to 2015.

Mode of Administration

- Subcutaneous administration, 3 doses over a 12-month period (months 0, 6 and 12).

Target Groups in Malaysia

- It is envisaged that when the vaccine is registered for use the target groups in Malaysia will be young children. Catch-up immunisation for older age-groups with high disease burden may be necessary to control dengue. Disease-reporting data would be required to identify age groups for catch-up immunisations and determine immunisation strategies.

- Travellers from non-endemic countries to tourist destinations with high risk of dengue transmission. This will also depend on the number and time interval between doses, which will limit this vaccine to selected populations.
Evidence for Effectiveness

- Current 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 are likely to 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 lead vaccine candidate by Sanofi Pasteur (CYD tetravalent) is a major milestone which showed acceptable safety and neutralising antibody immunogenicity profile.

- The Asian Phase III trial evaluated the efficacy and safety of Sanofi’s tetravalent dengue vaccine candidate 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 conducted on 20,875 children aged 9-16 across 5 countries in Latin America – Brazil, Columbia, Honduras, Mexico and Puerto 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. That might make the vaccine especially useful in endemic areas, rather than as a vaccination for tourists.

Phase IV trials will be necessary for long-term follow-up of the duration of protection, vaccine safety and impact on dengue transmission, among other issues.

References

Enterovirus 71 (EV71)

Introduction

Enterovirus 71 (EV71) is a member of the Enterovirus genus of the Picornaviridae family. It is one of the causative pathogens of hand-foot-and-mouth disease (HFMD) and the most common aetiological agent isolated from HFMD patients complicated with neurological disorders. EV71 has become an increasingly important neurotropic enterovirus in the post-poliomyelitis 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, pulmonary complications and fatal consequences. HFMD is a major emerging infectious disease in Asia-Pacific region, with increasing incidence over the past 2 decades and an important public health issue. HFMD has taken a significant toll across SouthEast Asia, affecting approximately 2,000,000 children every year.

EV71 is divided into 3 genotypic groups on the basis of VP1 sequence: A, B, and C where some viral genotypic subgroups seem to have massive potential for explosive epidemics, whereas others have more-indolent, low-level circulation. Effective antiviral agents and vaccines against this virus are currently still under development. Vaccines being developed include inactivated whole-virus, live attenuated, sub-viral particle, and DNA 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.

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 Coxsackievirus A16 were the main aetiological viruses isolated and more than one sub-genogroup of EV71 co-circulate in the past outbreaks in the country.
Vaccines

- Currently no vaccine is registered.

Various vaccine candidates have been developed. Several areas in EV71 vaccine development must be addressed before the clinical trials, including the selection of vaccine strain, standardisation of the procedure for quantifying neutralising antibody (NTAb) and antigen, establishment and application of a reference standard and biological standards, development of animal models for the evaluation of protective efficacy, and identification of the target patient population. 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 companies in mainland China (Beijing Vigoo Biological Co Ltd, Sinovac Biotech Ltd and Institute of Medical Biology, Chinese Academy of Medical Science (CAMS) have recently completed Phase III trials for the vaccines they developed. Two other vaccines, developed by the National Health Research Institutes (NHRI) of Taiwan and Inviragen Pte Ltd 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.

Vaccines Available in Malaysia

- None

Mode of Administration

- Intramuscular administration and various dosage regimens 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

- Published clinical trial results indicate that the inactivated EV71 vaccines have good safety profile and immunogenicity in the target population (infants) and confer a relatively high rate of protection against EV71 infection-related diseases.

References

5. Liang, Zheng-Lun; Mao, Quan-Ying; Wang, Yi-Ping; Zhu, Feng-Cai; Li, Jing-Xin; Yao, Xin; Gao, Fan; Wu, Xing; Xu, Miaow; Wang, Jun-Zhi. Progress on the research and development of inactivated EV71 whole-virus vaccines. Hum Vaccin & Immunother 9 (8), 2013 Jun 6
Adult Immunisation for Special Groups
Adults Who Have Missed Childhood Vaccination

Table 21.1
Recommended Vaccines

All adults should complete a primary series of the following vaccines & toxoids if they have not done so during childhood.

<table>
<thead>
<tr>
<th>Adults: Age group</th>
<th>Vaccine recommended</th>
<th>Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adults</td>
<td>Tetanus</td>
<td>Combined tetanus, diphtheria and pertussis (Tdap): 1st dose of Tdap followed by 2nd dose of Td given 4 weeks later &amp; 3rd dose of Td 6-12 months after 2nd dose. Booster (Td): every 10 years</td>
<td>Doses need not be repeated when vaccine schedule delayed. Persons with uncertain histories of receiving diphtheria, tetanus and pertussis vaccination should receive the full primary vaccination schedule and boosters</td>
</tr>
<tr>
<td></td>
<td>Diphtheria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pertussis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All adults</td>
<td>Poliomyelitis</td>
<td>A single booster dose of parenteral Polio vaccine every 10 years</td>
<td>There are still pockets of polio outbreaks in certain countries including Indonesia and the Indian subcontinent</td>
</tr>
<tr>
<td>Adults aged 18-64 years</td>
<td>Measles</td>
<td>2 doses of measles-mumps-rubella (MMR) live vaccine; given at least 1 month apart</td>
<td>Recommended if no history of physician-documented infection, laboratory evidence of immunity</td>
</tr>
<tr>
<td></td>
<td>Mumps</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Elderly and Patients with Chronic Illnesses

#### Table 21.2
Immunisations for the Elderly Patients

<table>
<thead>
<tr>
<th>Vaccines recommended</th>
<th>Indications</th>
<th>Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumococcal polysaccharide (PPSV23)</strong></td>
<td>All adults 60 years and above who are previously unvaccinated or of unknown vaccination status</td>
<td>A 2nd dose should be given to anyone above 60 years or older, previously vaccinated before the age 60 if 5 years or more have elapsed since 1st vaccination</td>
<td>Person who have not received vaccination within the last 5 years and was &lt;60 years of age at time of vaccination should be vaccinated</td>
</tr>
</tbody>
</table>
| **Influenza** | All elderly ≥50 years  
All residents of nursing homes or chronic care facilities | 1 dose administered annually | Vaccination can be given throughout the year  
Use the most recent formulation |
| **Zoster** | All elderly ≥60 years old regardless of report of prior zoster infection | 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 |
| **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
**Elderly and Patients with Chronic Diseases**

<table>
<thead>
<tr>
<th>Category</th>
<th>Vaccines recommended</th>
<th>Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly (≥60 years old) in particular residents of nursing homes and other chronic care facilities</td>
<td>Influenza*</td>
<td>Annual vaccination</td>
<td>Vaccination can be given throughout the year</td>
</tr>
<tr>
<td></td>
<td>Pneumococcal</td>
<td>No optimal time in Malaysia</td>
<td>Use the most recent formulation</td>
</tr>
<tr>
<td></td>
<td>Zoster</td>
<td>To be given if not vaccinated before or unknown vaccination status</td>
<td>Person who have not received vaccination within the last 5 years and was &lt;60 years of age at time of vaccination should be vaccinated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single dose for persons who have had previous varicella (chickenpox) infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with chronic illnesses (eg chronic pulmonary, cardiac, renal and liver disease, diabetes mellitus)</td>
<td>Pneumococcal</td>
<td>Please refer to relevant sections</td>
<td>Hepatitis B for end-stage renal disease, haemodialysis</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatitis B (for end-stage renal disease, haemodialysis)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Influenza vaccination is strongly recommended for all adults 50 years and above.
Table 21.4
Recommended Vaccination for Patients with Chronic Diseases

Patients with chronic diseases (renal failure, liver diseases, chronic lung disease, cardiac involvement, diabetes mellitus, asplenia) have limited defects of the immune system and a higher risk of infection. Therefore, patients with such pathologies should be immunised according to the routine immunisation schedules. The efficacy of immunisation decreases with disease progression; for this reason, these patients should be immunised as soon as possible. These patients may need additional doses or higher doses to provide them with adequate protection.

<table>
<thead>
<tr>
<th>Types of Vaccine</th>
<th>Chronic Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Td/Tdap)</td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td></td>
</tr>
<tr>
<td>HPV (female &amp; male)</td>
<td></td>
</tr>
</tbody>
</table>
### Special Groups

#### Types of Chronic Diseases

- Diabetes
- Chronic liver disease
- Asplenia (including splenectomy & persistent complement component deficiencies)
- Heart disease and chronic lung diseases
- Kidney diseases, ESRF, dialysis patients
- Immuno-compromised patients (excluding HIV)

#### Influenza

- 1 dose (inactivated influenza vaccine)

#### Tetanus, diphtheria, pertussis (Td/Tdap)

- Substitute 1 time dose of Tdap for Td booster
- Boost with Td every 10 years

#### Varicella

- 2 doses
- Contraindicated

#### HPV (female & male)

- As recommended for the general population

#### Pneumococcal vaccine

1. Asplenia, kidney disease and immunocompromised patients: PCV13 followed by PPV23 after 6-12 months
2. Diabetes, chronic liver disease heart disease and chronic lung disease: 1 dose PCV13

#### Meningococcal (1 or more doses)

- 1 or 2 doses
- Contraindicated

#### Hepatitis A

- Post HSCT only

#### Hepatitis B

- 1 or 2 doses
- Contraindicated

#### Haemophilus influenzae type b (Hib)

- Post HSCT only

#### MMR

- 1 or 2 doses
- Contraindicated

#### Zoster

- 1 dose
- Contraindicated

---

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 vaccination 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 indications)

**Note:** Inactivated vaccines generally are acceptable (eg pneumococcal, meningococcal, and inactivated influenza vaccine) and live vaccines generally are avoided in persons with immune deficiencies or immunocompromised conditions.
Healthcare Workers (HCWs)

On the basis of documented nosocomial transmission, HCWs are considered to be at significant risk for acquiring and transmitting the following vaccine preventable infections.

**Note:** The category of healthcare workers (HCWs) include persons who provide healthcare to patients or work in institutions that provide patient care e.g. Doctors, pharmacists, 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.
### Table 21.5
**Recommended Vaccines for Healthcare Workers (HCWs)**

The following vaccinations are **strongly recommended among HCWs**:

<table>
<thead>
<tr>
<th>Category of HCW</th>
<th>Vaccines recommended</th>
<th>Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HCW&lt;br&gt;Includes all workers and students directly involved in patient care or the handling of human tissue</td>
<td>Hepatitis B</td>
<td>Should be given as soon as feasible&lt;br&gt;Give 3 dose series (For details refer to page 62)</td>
<td>Post vaccination serologic testing for antibodies recommended</td>
</tr>
<tr>
<td>Measles, mumps and rubella</td>
<td>1 vaccination (2 doses) before onset of career&lt;br&gt;MMR vaccine preferred&lt;br&gt;Booster doses not necessary</td>
<td></td>
<td>Indicated for HCWs who do not have documented vaccination, physician diagnosed infection or serologic evidence of immunity Not indicated in pregnant women</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td>Annual vaccination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pertussis (Tdap)</td>
<td>HCWs should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap</td>
<td>Tdap can be administered regardless of interval since the last tetanus or diphtheria containing vaccine</td>
</tr>
<tr>
<td></td>
<td>Varicella</td>
<td>Vaccination (Two 0.5mL S/C doses 4-8 weeks apart) should be given before posting to unit&lt;br&gt;Booster doses not necessary</td>
<td>Pre vaccination serologic testing is cost effective in those who do not have a reliable history of varicella infection or serologic evidence of immunity</td>
</tr>
</tbody>
</table>
Special Groups

The following vaccines are **not routinely recommended for HCWs** (exceptions listed in parenthesis)

- **Bacillus Calmette-Guerin (BCG) vaccine**: 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 vaccine**: consider for HCWs who work in remote Indigenous communities or with Indigenous children

- **Typhoid vaccine**: considered in workers in microbiology laboratories who frequently work with S. Typhi.

- **Meningococcal polysaccharide vaccine**: indicated for laboratory personnel working frequently with *N. meningitides*.

- **Vaccinia vaccine**: indicated only for laboratory workers involved with orthopox viruses and certain HCWs involved in clinical trials of vaccinia recombinant vaccines.

- **Anthrax vaccine**: indicated for laboratory personnel working with *Bacillus anthracis*.

- **Rabies vaccine**: pre-exposure vaccination only indicated for laboratory workers directly involved with testing or isolating rabies virus.
Immunocompromised Patients

Table 21.6
Vaccination for Individuals with Splenectomy or Functional Asplenia

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Recommendations</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyvalent pneumococcus, meningococcus, Hib</td>
<td>To be given 2 weeks before or 2 weeks after splenectomy for optimal response</td>
<td>Booster dose is recommended every 5 years for pneumococcus and every 3-5 years for meningococcus</td>
</tr>
<tr>
<td></td>
<td>Vaccination may be considered upon discharge if patient is expected not to return for follow-up</td>
<td></td>
</tr>
<tr>
<td><strong>Use if indicated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG, hepatitis A, hepatitis B, influenza, MMR, inactivated polio vaccine, rabies, Td, typhoid and varicella</td>
<td>Hepatitis A and B vaccines are recommended for sickle cell disease or thalassaemias undergoing splenectomy</td>
<td></td>
</tr>
</tbody>
</table>
### Table 21.7
**Vaccination for Immunocompromised Patients**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>HIV</th>
<th>Immuno-suppressed</th>
<th>Renal failure</th>
<th>Diabetes mellitus</th>
<th>Chronic alcoholism</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>C</td>
<td>C</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Hep A</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Hep B</td>
<td>R – double dose</td>
<td>UI – double dose</td>
<td>R – double dose</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Hib</td>
<td>UI</td>
<td>R</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>HPV</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Influenza (Inactivated)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>MMR</td>
<td>UI*</td>
<td>C</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>IPV</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Pneumococcus (PCV13 or PPSV23)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Rabies</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Td</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Inactivated typhoid and cholera</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Varicella</td>
<td>UI*</td>
<td>C</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
<tr>
<td>Zoster</td>
<td>C</td>
<td>C</td>
<td>UI</td>
<td>UI</td>
<td>UI</td>
</tr>
</tbody>
</table>

C – Contraindicated  
R – Recommended  
UI – Use if indicated

*Contraindicated in AIDS
Note 1: Immunisation for individuals with suppressed immunity due to disease or treatment

- The following groups of individuals should not receive live vaccines:
  - Patients receiving high dose oral or intravenous steroids or other immunosuppressive treatment including total body or lymphoid irradiation. Daily doses of corticosteroids in excess of 0.5mg/kg/day of prednisolone or equivalent for >14 days are associated with significant immunosuppression. Lower doses may also be associated with an impaired immune response. For patients receiving the above high dose steroids or who have received prolonged or extensive therapy topically, orally or by inhalation, live vaccines should be postponed until 3 months after cessation of therapy.
  - Patients with lymphoma, leukaemia or other malignancies of the reticuloendothelial system. These include patients in remission who have received chemotherapy within the last 3 months or those whose remission status may not be clear.
  - Patients with impaired immunity including severe combined immunodeficiency syndrome and HIV.

Inactivated vaccines (such as pertussis and hepatitis A), modified vaccines (such as diphtheria and tetanus vaccines) and subunit vaccines (such as Hib and hepatitis B) may not be harmful to the above recipients and can be safely given but may be of doubtful efficacy.
Note 2: Vaccination of HIV-infected individuals

Vaccination of HIV-infected individuals poses different problems. The immune status of the individual can range from minimal to profound deficiency. There is a risk that live vaccines may cause severe infection. The immune response to vaccines may be inadequate and higher or more frequent doses may be required. It is highly likely that individuals with good CD4 counts will respond well to vaccines.

- Pneumococcal infection is a frequent cause of morbidity. Pneumococcal polysaccharide vaccine may be given although there may be limited efficacy. A single dose of conjugate PCV13 is recommended followed by PPV23 8 weeks later.

- Influenza vaccine may also be given to individuals at risk as the benefit outweighs the risk.

- Recombinant Hepatitis B vaccines are safe to use but the normal dosage should be doubled and given on 3 occasions. It is recommended that the antibody response be monitored. (target anti-HBs level >10mIU/mL)

- Hepatitis A vaccine has not been evaluated in this population but may be given if indicated.

- BCG vaccine should NOT be given.

- For travel – live attenuated typhoid or yellow fever vaccines should NOT be given. Meningococcal, typhoid, cholera and rabies vaccines are safe with the usual indications.
Note 3: Vaccination for haemodialysis and chronic renal failure patients

The above persons are at high risk of infection with HBV and routine serologic screening is advised. Susceptible patients should receive 3 doses of HBV vaccine of double strength. Post-vaccination antibody screening is recommended. Revaccination is considered for non-responders and if anti-HBs levels remain <10mIU/mL. As these patients are at increased risk of lower respiratory infections, pneumococcal and influenza vaccinations are also recommended.

Note 4: Chronic immunosuppressive therapy

This population includes inflammatory diseases and autoimmune disorders receiving chronic immunosuppressive treatments. Patients with autoimmune disorders in remission and not on treatment are not considered significantly immunocompromised and may receive routine immunisations. The use of monoclonal antibodies and biologic drugs including anti-tumour necrosis factor (TNF) agents may result in prolonged immunosuppression and the use of live vaccines should be avoided. The use of inactivated vaccines is not contraindicated. In general however, all appropriate inactivated vaccines should be administered 14 days before initiation of treatment or 3 months after cessation of treatments to establish immunogenicity.
### Table 21.8
**Passive Immunisation for Immunocompromised Persons**

<table>
<thead>
<tr>
<th>Subgroup at risk</th>
<th>Ig</th>
<th>Recommendation</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hypogamma-globulinaemia</td>
<td></td>
<td>0.4-0.6gm/kg every 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Secondary hypogamma-globulinaemia with recurrent severe infections (&gt;2 episodes/year)</td>
<td>IV NHlg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immuno-compromised patients</td>
<td>IM NHlg</td>
<td>Measles: IM 0.25-0.5mL/kg (max 15mL) administered as soon as possible (within 6 days after exposure) regardless of previous vaccination status</td>
<td>IM NHlg may not be necessary for patients who are receiving IV NHlg at regular intervals and the last dose was administered within 3 weeks of exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis A: IM 0.02mL/kg (max 15mL) administered as soon as possible (within 2 weeks of exposure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Varicella-zoster: IM 125units/10kg (max 625 units) administered as soon as possible or within 96 hours of contact</td>
<td>Definition of contact: Household contact, close contact indoors &gt;1 hour Sharing 2-4 bed hospital cubicle/room Prolonged direct face-to-face contact (eg doctor/nurse and patient)</td>
</tr>
<tr>
<td>Subgroup at risk</td>
<td>Ig</td>
<td>Recommendation</td>
<td>Additional comments</td>
</tr>
<tr>
<td>---------------------------------------------------------------------</td>
<td>--------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Hepatitis B:</strong></td>
<td>HB Ig</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If Hepatitis B vaccine series has not been started, a 2nd dose of HB Ig should be administered one month later (for percutaneous/mucous membrane exposure) or 3 months after sexual exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hep B vaccine should be given at a different site if used simultaneously with HB Ig or within 1 week of exposure</td>
<td></td>
</tr>
<tr>
<td><strong>Tetanus:</strong></td>
<td>T Ig</td>
<td>For wound &lt;24 hours IM 250 units</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For wound &gt;24 hours or heavy contamination – IM 500 units</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inadequate tetanus vaccination is defined as less than 2 doses of tetanus vaccine previously</td>
<td></td>
</tr>
<tr>
<td><strong>Rabies:</strong></td>
<td>R Ig</td>
<td>20IU/kg, up to half to be infiltrated around the wound and remaining to be given IM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For non-vaccinated persons: IM rabies vaccine on days 0, 3, 14, 28</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For previously vaccinated persons: IM rabies vaccine on days 0, 3</td>
<td></td>
</tr>
</tbody>
</table>
### Table 21.9
Vaccination for Blood and Marrow Transplant Recipients (Allogeneic and Autologous)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Time after transplant</th>
<th>Chronic GVHD#</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 months</td>
<td>14 months</td>
<td>18 months</td>
</tr>
<tr>
<td><strong>Inactivated vaccine or toxoid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, tetanus, pertussis</td>
<td>DTaP</td>
<td>DT</td>
<td>DT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td>Hib conjugate</td>
<td>Hib conjugate</td>
<td>Hib conjugate</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>Influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2 doses 4 weeks apart)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep B</td>
<td>Hep B</td>
<td>Hep B</td>
<td>Hep B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>Use if indicated - 3 doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated polio</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcus</td>
<td>Use if indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2 doses of quadrivalent vaccine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine</td>
<td>12 months</td>
<td>14 months</td>
<td>18 months</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>Time after transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live-attenuated virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BCG</td>
<td>Not recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella (live)</td>
<td>Limited data regarding safety and efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster (live)</td>
<td>Limited data regarding safety and efficacy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTES**

- **Pneumococcal vaccine**
  - There are 2 types of pneumococcal vaccine – conjugate vaccine (PCV13) and polysaccharide vaccine (PPSV23).
  - The PCV13 is more immunogenic and preferred but the spectrum of protection is narrower.
  - The PPSV23 covers 23 strains but is less immunogenic and may elicit inadequate response. It may be beneficial to use PPSV23 as the fourth dose to broaden the immune response.

- Attenuated diphtheria vaccine
  - Td or Tdap may be associated with lack of response. Full toxoid vaccines should be used where possible.
  - Foreign travel
  - 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 vaccine.

Donor vaccination may improve the immunity of patients 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.

# Whether to vaccinate if the patient has chronic graft versus host disease (GVHD).
### Table 21.10
Vaccination for Solid Organ Transplant Recipients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Full immunisation</th>
<th>Visit 1</th>
<th>Visit 2 (1-2 months after visit 1)</th>
<th>Visit 3 (6 months after visit 2)</th>
<th>Booster dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactivated vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DT</td>
<td>3 doses</td>
<td>DT</td>
<td>DT</td>
<td>DT</td>
<td>DT</td>
<td>Booster every 10 years For those with no previous vaccination history, to give first dose as DTaP</td>
</tr>
<tr>
<td>Hib conjugate</td>
<td>1 dose</td>
<td></td>
<td>Recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>3 doses</td>
<td>Hep B</td>
<td>Hep B</td>
<td>Hep B</td>
<td>Booster if titre &lt;10mIU/mL</td>
<td>High dose formulation required; check titres 4-8 weeks after last dose</td>
</tr>
<tr>
<td><strong>Hepatitis A</strong></td>
<td>2 doses, for patients at risk only</td>
<td>Hep A</td>
<td></td>
<td>Hep A</td>
<td></td>
<td>Patient at risk include those for liver transplant, chronic liver disease and at risk of Hep A exposure</td>
</tr>
<tr>
<td><strong>Live vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>Up to 2 doses, for pre-transplant only</td>
<td>MMR</td>
<td>MMR</td>
<td></td>
<td></td>
<td>Not recommended after transplant</td>
</tr>
<tr>
<td>Varicella</td>
<td>2 doses</td>
<td>Varicella</td>
<td></td>
<td>Varicella</td>
<td></td>
<td>Not recommended after transplant, for those who are seronegative only</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Doses/Booster</td>
<td>Additional Information</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>3 doses</td>
<td>Use if indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Influenza</strong></td>
<td></td>
<td>Recommended annually</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPV</td>
<td>3 doses + 1 booster for at risk patient</td>
<td>IPV IPV IPV Recommended for patients at risk only – in endemic areas or occupational risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meningococcus</strong></td>
<td>1-2 doses, at risk patient only</td>
<td>Meningococcal Booster dose 5 years later Patient at risk include those with asplenia, travel exposure and college students</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pneumococcus</strong></td>
<td>2 doses</td>
<td>PCV 13 PPV 23 Booster dose 5 years later</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Live vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MMR</strong></td>
<td>Up to 2 doses, for pre-transplant only</td>
<td>MMR MMR Not recommended after transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Varicella</strong></td>
<td>2 doses, for pre-transplant and at risk only</td>
<td>Varicella Varicella Not recommended after transplant, for those who are seronegative only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Travellers

#### Table 21.11

**Vaccination Summary for Travellers**

<table>
<thead>
<tr>
<th>Category</th>
<th>Vaccine</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory vaccination</td>
<td>Yellow fever for all travellers traveling to or from yellow fever endemic countries&lt;br&gt;See page 181 for advice for Hajj and Umrah pilgrims</td>
<td>These vaccines are legal requirements for travel&lt;br&gt;Failure to obtain vaccines could result in non-entry/quarantine in destination as well as home country&lt;br&gt;Countries requiring yellow fever vaccination for entry do so in accordance with the International Health Regulations&lt;br&gt;Country requirements are subject to change at any time. Updates can be found at: <a href="http://www.who.int/ith">www.who.int/ith</a></td>
</tr>
<tr>
<td>Routine vaccination</td>
<td>Diphtheria/tetanus/pertussis&lt;br&gt;Hepatitis B&lt;br&gt;Measles/mumps/rubella&lt;br&gt;Poliomyelitis</td>
<td>Although not mandatory all travelers are generally advised to ensure that they have these necessary vaccination and boosters</td>
</tr>
<tr>
<td>Selective use for travelers</td>
<td>Cholera&lt;br&gt;Influenza&lt;br&gt;Hepatitis A&lt;br&gt;Japanese encephalitis&lt;br&gt;Lyme disease&lt;br&gt;Meningococcal&lt;br&gt;Pneumococcal&lt;br&gt;Rabies&lt;br&gt;Tick-borne encephalitis&lt;br&gt;BCG&lt;br&gt;Typhoid</td>
<td>Recommendations for these vaccines depend on the countries of destination, the current outbreak situation at the time of travel, the purpose for travel, the intended length of stay and the health status of the traveler&lt;br&gt;As recommendations will change from time to time, it is prudent to access the latest advisories from the following sites maintained by the CDC and WHO wwwnc.cdc.gov/travel/ <a href="http://www.who.int/ith">www.who.int/ith</a></td>
</tr>
</tbody>
</table>
The following websites provide updated information on immunisation for travellers 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/)
<table>
<thead>
<tr>
<th>Category</th>
<th>Vaccines recommended</th>
<th>When to give</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel working exclusively with non-feral rodents and rabbits from approved sources and cold blooded vertebrates</td>
<td>BCG (if Mantoux negative) Tetanus</td>
<td>Vaccination at time of employment A tetanus booster is recommended every 10 years</td>
<td>Health check-up at time of employment</td>
</tr>
<tr>
<td>Personnel working or exposed to feral animals and purpose bred laboratory animals from non approved sources and farm animals</td>
<td>BCG (if Mantoux negative) Tetanus</td>
<td>Vaccination at time of employment A tetanus booster is recommended every 10 yrs</td>
<td>Health check-up at time of employment</td>
</tr>
<tr>
<td>Personnel exposed to cats, dogs, feral animals from populations known to be potential carriers of rabies</td>
<td>BCG (if Mantoux negative) Tetanus Rabies</td>
<td>Vaccination at time of employment A tetanus booster is recommended every 10 yrs A rabies booster is recommended every 2 yrs</td>
<td>Health check-up at time of employment</td>
</tr>
<tr>
<td>Category</td>
<td>Vaccines</td>
<td>When to give</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Personnel working with nonhuman primates</td>
<td>BCG (if Mantoux negative) Tetanus Measles</td>
<td>Vaccination at time of employment</td>
<td>Health check-up at time of employment</td>
</tr>
<tr>
<td>Personnel involved in animal care whether laboratory animals or primates</td>
<td>BCG (if Mantoux negative) Tetanus Rabies Measles</td>
<td>Vaccination at time of employment</td>
<td>Health check-up at time of employment</td>
</tr>
<tr>
<td>Personnel with exposure to poultry, domestic, non domestic birds or pigs</td>
<td>Influenza JE</td>
<td>Vaccination at time of employment</td>
<td>Note that the best protection against influenza is by having good personal hygiene and a healthy lifestyle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>An annual vaccination is recommended</td>
<td>Workers handling birds should also take the general precautionary measures against avian influenza</td>
</tr>
</tbody>
</table>
## Miscellaneous Other Groups

### Table 21.13
Recommended Vaccines

<table>
<thead>
<tr>
<th>Category</th>
<th>Vaccine(s) Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prisoners</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Men who have sex with men (MSM)</td>
<td>Hepatitis A and B</td>
</tr>
<tr>
<td></td>
<td>Quadrivalent HPV</td>
</tr>
<tr>
<td>Injecting drug users (IDU)</td>
<td>Hepatitis A and B</td>
</tr>
<tr>
<td>People who work with children</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>MMR (if non immune)</td>
</tr>
<tr>
<td></td>
<td>Pertussis (Tdap)</td>
</tr>
<tr>
<td></td>
<td>Varicella (if non immune)</td>
</tr>
<tr>
<td>Carers</td>
<td>Hepatitis A and B, Influenza</td>
</tr>
<tr>
<td>- carers for persons with developmental disabilities</td>
<td>Influenza</td>
</tr>
<tr>
<td>- staff of nursing homes and long term care facilities for persons of any age</td>
<td>MMR (if non immune)</td>
</tr>
<tr>
<td></td>
<td>Varicella (if non immune)</td>
</tr>
<tr>
<td>Emergency and essential service workers</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>- police/emergency workers/armed forces personnel/staff of correctional facilities, prison or detention centres</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>MMR (if not immune)</td>
</tr>
<tr>
<td></td>
<td>Tetanus (Td or Tdap)</td>
</tr>
</tbody>
</table>
Vaccination for Hajj and Umrah Pilgrimage

All pilgrims should be up-to-date with routine vaccinations. In addition, hepatitis A and B, influenza and typhoid vaccines are recommended. The most current vaccination requirements are available from the Saudi Arabian Ministry of Health website (www.moh.gov.sa/en/)

Meningococcal vaccine

Saudi Ministry of Health requires all pilgrims to receive the meningococcal vaccine. Hajj visa cannot 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

* Duration of protection is only 2 years for Mencevax® while for other vaccines the duration is between 3-5 years.
For further information or enquiry, please contact:

Malaysian Society of Infectious Diseases and Chemotherapy
c/o
Department of Medical Microbiology,
Faculty of Medicine, University Kebangsaan Malaysia,
Hospital Univeristy Kebangsaan Malaysia,
Jalan Yaacob Latif,
Bandar Tun Razak, Cheras,
56000, Kuala Lumpur, Malaysia.