4.23 YELLOW FEVER

4.23.1 Virology

Yellow fever is a viral haemorrhagic fever caused by an RNA flavivirus. The virus is transmitted by mosquitoes (predominantly *Ae. aegypti*) through jungle (between non-human primates and mosquitoes) and urban (between humans and mosquitoes) zoonotic transmission cycles. In Africa, an intermediate transmission cycle exists between humans or non-human primates and *Aedes* species mosquitoes that breed in tree holes in savannah areas.¹

4.23.2 Clinical features

The clinical spectrum of yellow fever varies from a non-specific febrile illness to fatal haemorrhagic fever.² After an incubation period of 3 to 6 days, the disease begins abruptly with fever, prostration, myalgia and headache. The patient appears acutely ill with congestion of the conjunctivae; there is an intense viraemia during this ‘period of infection’, which lasts 3 to 4 days.² This may be followed by the ‘period of remission’, in which the fever and symptoms settle over 24 to 48 hours, during which the virus is cleared by immune responses.²

Approximately 15 to 25% of patients may then relapse with a high fever, vomiting, epigastric pain, jaundice, renal failure and haemorrhage, referred to as ‘the period of intoxication’.² These complications can be severe, and reflect the viscerotropic nature of the yellow fever virus (its ability to infect the liver, heart and kidneys). The case-fatality rate varies widely, but can be more than 20% in local populations.³

4.23.3 Epidemiology

Yellow fever virus occurs in tropical and subtropical regions of Africa and South America where it is endemic and intermittently epidemic.

The epidemiology of yellow fever is dynamic due to changes in climate, such as rainfall patterns, and human factors such as migration and air travel.¹ West Africa has the highest burden of yellow fever disease, accounting for 90% of all yellow fever cases reported between 1985 and 2009. The remainder of cases occur in other regions of Africa and South America.⁴ In 2014, 21 cases of yellow fever, including 12 deaths, were reported to the World Health Organization (WHO) from three countries: the Democratic Republic of Congo, Brazil and Peru. In 2006, the WHO introduced the Yellow Fever Initiative with the aim to control and eliminate epidemic yellow fever in Africa by including yellow fever vaccine in routine childhood immunisation programs and implementing mass vaccination campaigns. In endemic areas where high vaccination coverage has been achieved, the occurrence of yellow fever outbreaks has decreased substantially. A similar approach has been taken in South America.⁵

The risk of susceptible travellers acquiring yellow fever varies considerably with season, location, duration of travel and utilisation of mosquito avoidance measures. There have been reported cases of yellow fever, all fatal, in unvaccinated travellers to Africa and South America.⁶ Updated information regarding yellow fever virus activity and/or risk in travel destinations should be sought from a reputable source prior to travel (for example, *Health information for international travel* [the ‘Yellow book’] published by the US Centers for Disease Control and Prevention, available at [www.cdc.gov/travel/yellowbook](http://www.cdc.gov/travel/yellowbook)).⁷

4.23.4 Vaccine

- **Stamaril** – Sanofi-Aventis Australia Pty Ltd (live attenuated yellow fever virus [17D strain]). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains ≥1000 IU of yellow fever virus; 16.0 mg lactose; 8.0 mg sorbitol; 0.833 mg L-histidine hydrochloride. May contain traces of egg proteins.
Yellow fever vaccine is a live, freeze-dried preparation of attenuated 17D strain yellow fever virus cultured in, and harvested from, embryonated chicken eggs. The vaccine does not contain antibiotics, preservatives or gelatin.

There are no studies that directly assess the efficacy of yellow fever vaccine. However, immunogenicity is used as a surrogate for protection, with thresholds for protective immunity defined as either $\log_{10}$ neutralisation index (LNI) $>0.7$, or a titre of $>1:10$ using plaque reduction neutralisation tests. Following a single dose of yellow fever vaccine, protective levels of neutralising antibodies are achieved in approximately 90% of healthy adult vaccine recipients by day 14, and in virtually all recipients by day 28. In children, the proportion of vaccine recipients who achieve protective yellow fever antibody levels following a single dose of vaccine is similar to that in adults. One randomised trial suggested lower seroconversion rates against yellow fever virus in children <2 years of age (70%); however, this was when yellow fever vaccine was co-administered with MMR vaccine. In comparison, 87% of children who received yellow fever and MMR vaccines separated by an interval of 30 days or more seroconverted. This study did not report on the proportion of participants with protective levels of neutralising antibodies based on commonly applied definitions.

Immunogenicity studies in individuals with underlying medical conditions are limited. Some data suggest that pregnant women and HIV-infected persons do not respond optimally to yellow fever vaccination. The proportion of recipients who achieved protective levels of neutralising antibodies was lower in women who received yellow fever vaccine in their third trimester of pregnancy (38.6%) than in non-pregnant women of child-bearing age and other adults (81.5–93.7%). However, a better response to the yellow fever vaccine was reported in a separate study of women vaccinated in their first trimester of pregnancy, suggesting that antibody response to vaccination in pregnant women may be dependent on length of gestation. Two studies reported lower rates of neutralising antibodies among HIV-infected persons compared with uninfected controls.

Although some observational studies have reported seroconversion rates in HIV-infected persons similar to those reported in healthy adults (>90%), the number of participants in these studies was small and there were no healthy controls. When reported, CD4+ counts of HIV-infected subjects were >200 cells per $\mu$L. A number of studies found higher antibody titres were associated with higher CD4+ counts and lower HIV RNA levels.

Data on the immunogenicity of yellow fever vaccine in persons who are immunocompromised, other than with HIV infection, is limited to a few small low quality studies and case reports. A reduced immune response to yellow fever vaccine has been reported among persons receiving immunosuppressive therapy for rheumatoid disease.

Immunity to yellow fever virus following a single dose of yellow fever vaccine is expected to be life-long in the majority of healthy vaccine recipients. Protective levels of neutralising antibodies have been detected in 75 to 100% of healthy adults from endemic and non-endemic yellow fever areas when measured ≥10 years after primary immunisation (ranging from 10 to 69 years post vaccination). Although yellow fever disease has occurred in vaccine recipients, this has only been reported in persons living in highly endemic areas. A study from Brazil showed that among 459 persons with laboratory-confirmed yellow fever who reported previous vaccination, 432 (94%) had yellow fever ≥10 years after vaccination. This indicates probable secondary vaccine failure due to waning immunity, although primary vaccine failure (poor initial immune response) may also have contributed.

There are few studies which have assessed the duration of immunity in groups who do not respond optimally to primary yellow fever vaccination. A cohort study of HIV-infected individuals that measured yellow fever neutralising antibodies over many years reported 23% of patients lost protective levels of neutralising antibody within 1 to 10 years of vaccination, almost twice the proportion among HIV-uninfected individuals.
A booster dose of yellow fever vaccine has been shown to be effective in producing protective levels of yellow fever neutralising antibodies in those whose response to their primary vaccine dose was low or negative.  

4.23.5 Transport, storage and handling
Transport according to National vaccine storage guidelines: Strive for 5. Store at +2°C to +8°C. Do not freeze. Protect from light.

Stamaril must be reconstituted by adding the entire contents of the diluent syringe to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine must be used within 1 hour.

4.23.6 Dosage and administration
The dose of yellow fever vaccine for children and adults is 0.5 mL, to be given by either IM or SC injection.

Co-administration with other vaccines
Inactivated vaccines and oral live vaccines relevant to travel (e.g. cholera, typhoid) can be given with, or at any time before or after, yellow fever vaccine.

If administration of both yellow fever and other parenteral live vaccines is indicated, the vaccines can be given either on the same day or at least 4 weeks apart. Studies of yellow fever vaccine administered at the same time as other live vaccines, including Japanese encephalitis, BCG and monovalent measles vaccines, have shown no impact on the immune response to any of the vaccine antigens. Although one Brazilian study suggested the co-administration of yellow fever and MMR vaccines results in lower seroconversion rates to the vaccine antigens than when the vaccines are administered at least 4 weeks apart (refer to 4.23.4 Vaccine above), further studies are required to determine the clinical significance of this finding. Yellow fever vaccine can be given at the same time as the Imojev Japanese encephalitis vaccine, using separate syringes and separate injection sites.

4.23.7 Recommendations

Children aged <9 months
Yellow fever vaccine is contraindicated in infants aged <9 months (refer to 4.23.9 Contraindications below).

Children aged ≥9 months and adults
Yellow fever vaccination can only be provided at Yellow Fever Vaccination Centres approved by the relevant state or territory health authorities (refer to ‘International travel requirements’ below).

A single dose of yellow fever vaccine is recommended for:

- persons ≥9 months of age travelling to, or living in, an area with a risk of yellow fever virus transmission. Information about the risk for specific destinations should be sought from a reputable source, such as the WHO or the Centers for Disease Control and Prevention, prior to travel.

- laboratory personnel who routinely work with yellow fever virus.

Vaccination is generally not recommended when travelling to an area where there is low potential for yellow fever virus exposure (i.e. no human yellow fever cases ever reported and evidence to suggest only low levels of yellow fever virus transmission in the past).

However, vaccination may be considered for travellers outside of the above groups under certain circumstances, for example, to meet specific countries’ vaccination requirements for travel (refer to ‘International travel requirements’ below).
Booster vaccination

In most individuals, a booster dose is not required as a single dose of yellow fever vaccine induces protective antibody levels that persist for many decades (refer to 4.23.4 Vaccine above).

A booster dose is recommended for those individuals who do not respond optimally to yellow fever vaccination (refer to 4.23.4 Vaccine above) if they are travelling to, or living in, an area with a risk of yellow fever virus transmission and 10 or more years have passed since their last dose. These individuals include:

- women who were pregnant when they received their initial dose of yellow fever vaccine, regardless of trimester
- persons who were infected with HIV when they received their initial dose of yellow fever vaccine (regardless of their degree of immunosupression at the time).

A booster dose should also be considered for travellers outside of the above groups under certain circumstances, for example, to meet specific countries’ vaccination requirements for travel (refer to ‘International travel requirements’ below) or due to a higher risk of yellow fever virus infection (e.g. if living in a high-risk location for an extended period of time or travelling to an area with ongoing outbreaks).

Laboratory workers with ongoing exposure to yellow fever virus should have neutralising antibody titres measured if 10 years or more have passed since their last vaccine dose to determine if a protective antibody level has been maintained. If antibody titres cannot be measured, a booster dose should be administered every 10 years.

Individuals who received a haematopoietic stem cell transplant after a dose of yellow fever vaccine should receive an additional vaccine dose prior to the next time they will be at risk of yellow fever virus infection, irrespective of the period since their last dose. The additional dose should preferably be administered after a period of 24 months has elapsed following the transplant. If the patient has ongoing graft-versus-host disease or remains on immunosuppressive therapy, vaccination should be delayed until the patient is sufficiently immunocompetent. (Refer also to 3.3.3 Vaccination of immunocompromised persons, ‘Haematopoietic stem cell transplant recipients’.)

International travel requirements

All those travelling to, or living in, countries with a risk of yellow fever virus transmission should be informed that the mosquito vectors of yellow fever usually bite during the day. They should be advised of the necessity for mosquito avoidance measures, even if vaccinated. These include the use of insect repellents, coils and sprays, the use of mosquito nets (preferably those that have been treated with an insecticide), and adequate screening of residential and work premises.

Under the International Health Regulations (2005) (IHR), many countries require travellers arriving from countries with a risk of yellow fever virus transmission to provide a valid International Certificate of Vaccination or Prophylaxis (ICVP) against yellow fever, or a valid letter of exemption, prior to entry. A country may require such documentation even for travellers who are only in transit through that country. This is because importation of the virus into these countries by an infected traveller could result in introduction and establishment of the virus in local *Ae. aegypti* mosquitoes. In 2014, the World Health Assembly of the WHO agreed to extend the validity of the ICVP from 10 years to the duration of the life of the vaccinated person, based on evidence demonstrating that a single dose of yellow fever vaccine provides protection for many decades in most individuals (refer to 4.23.4 Vaccine above). This change in the IHR took effect in June 2016 but yellow fever vaccination entry requirements for some countries may still vary.

It is recommended that the entry requirements for yellow fever vaccination for the countries a traveller intends to enter or transit through be confirmed prior to travel by contacting the country’s foreign missions in Australia.
Australia’s travel requirements

Australia strongly recommends that travellers >1 year of age entering Australia within 6 days of leaving a country on Australia’s list of yellow fever declared places, where they have stayed overnight or longer, have a valid ICVP with proof of valid yellow fever vaccination. Yellow fever vaccination and an ICVP can only be issued by accredited Yellow Fever Vaccination Centres approved by the relevant state or territory health authorities. The ICVP must record the name of the vaccinated individual, date of the vaccination (day–month–year sequence, with the month written in letters), the vaccine administered, the signature of the authorised health professional and the official stamp provided by the state or territory health authority.

Australia has adopted the WHO amendment to the IHR and as such, as of 16 June 2016, an ICVP is considered valid for the duration of the life of the vaccinated person. The certificate becomes valid 10 days after vaccination.

Travellers who do not have a valid certificate are provided with information on yellow fever and are recommended to promptly seek medical assessment if they develop relevant symptoms within 6 days of leaving a yellow fever declared place. A list of yellow fever declared places is available from the Australian Government Department of Health’s yellow fever fact sheet (www.health.gov.au/yellowfever).

Exemptions to vaccination

People with a true contraindication to yellow fever vaccine (refer to 4.23.9 Contraindications below) who intend to travel to countries with a risk of yellow fever virus transmission should obtain a dated and signed letter on letterhead stationery from an accredited Yellow Fever Vaccination Centre. The letter should clearly state the yellow fever vaccine is contraindicated on medical grounds and display the centre’s official stamp provided by the state or territory health authority. Medical exemption letters should be written for the current trip only. If exemption to yellow fever vaccination is required for any subsequent trips, a new medical exemption letter should be issued. The vaccination provider is also required to complete, stamp and sign the Medical Contraindications to Vaccination section of the ICVP. Arriving travellers who possess a medical exemption letter for yellow fever vaccination are provided with information on yellow fever and recommended to promptly seek medical assessment if they develop relevant symptoms.

If it is expected that the exemption to yellow fever vaccination will be required in another country where travel is planned, the traveller should contact the country’s foreign missions in Australia to ascertain if the letter needs to be in another language in addition to English.

4.23.8 Pregnancy and breastfeeding

Yellow fever vaccine is not recommended for pregnant women or for women breastfeeding infants aged <9 months, other than in exceptional circumstances.

As with all live attenuated virus vaccines, yellow fever vaccine should not routinely be given to pregnant women, unless there is a risk of exposure to the virus. Pregnant women should be advised against going to an area with a risk of yellow fever virus transmission. However, where travel to an at-risk area is unavoidable, such women should be vaccinated.13,34-36 Women who received their first dose of yellow fever vaccine while pregnant may require additional doses in the future if they remain at risk of yellow fever virus transmission (refer to 4.23.7 Recommendations above).

The yellow fever vaccine has been given to considerable numbers of pregnant women4,13,34 with no evidence of any adverse outcomes. Therefore, women vaccinated in early pregnancy can be reassured that there is no evidence of risk to themselves and very low (if any) risk to the fetus.4 Administration of yellow fever vaccine to women who are breastfeeding infants aged <9 months should be avoided, except in situations where exposure to yellow fever virus cannot be avoided or postponed.35,36 Although extremely rare, there have been several case reports of transmission of the
vaccine strain of yellow fever virus via breast milk resulting in probable vaccine-associated neurotropic disease in the infants (refer to 4.23.11 Adverse events below). On follow-up of these infants, their neurological development was considered normal.\textsuperscript{35,36}

Refer to 3.3 Groups with special vaccination requirements, Table 3.3.1 Recommendations for vaccination in pregnancy for more information.

4.23.9 Contraindications

Any person with a true contraindication to yellow fever vaccination should be advised against going to an area with a risk of yellow fever virus transmission. However, where travel to an at-risk area is unavoidable, such persons should be advised of the necessity for mosquito avoidance measures (refer to 4.23.7 Recommendations, ‘International travel requirements’ above).

Anaphylaxis to vaccine components

Yellow fever vaccine is contraindicated in persons who have had:

- anaphylaxis following a previous dose of the vaccine
- anaphylaxis following any vaccine component.

In particular, the vaccine is contraindicated in persons with a known anaphylaxis to eggs. Persons with a known allergy to eggs wishing to receive yellow fever vaccination should discuss this with either an immunologist/allergist or be referred to a specialised immunisation adverse events clinic. Contact a specialist travel medicine clinic or your local state or territory health authority for further details (refer to Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control).

Infants

Routine yellow fever vaccine is generally contraindicated in infants <9 months of age due to the risk of severe adverse events following vaccination (refer to 4.23.11 Adverse events below). However, countries experiencing a mass outbreak of yellow fever may elect to immunise infants from as young as 6 months of age.\textsuperscript{37}

Persons who are immunocompromised

As with all live viral vaccines, the yellow fever vaccine should generally not be given to people who are immunocompromised due to either disease or medical treatment. The vaccine can, however, be considered on a case-by-case basis taking into account factors such as risk of exposure and level of compromise (refer to 3.3.3 Vaccination of immunocompromised persons). There is a concern that immunocompromised individuals may not mount a sufficient immune response following vaccination and may be at risk of vaccine-related adverse events. However, there are few studies assessing yellow fever vaccine immunogenicity in these individuals (refer to 4.23.4 Vaccine above) and an association with serious adverse events has only been demonstrated for individuals with thymus disorders (refer to 4.23.11 Adverse events below).

Yellow fever vaccine can be given to certain persons infected with HIV who are at risk of yellow fever virus infection (refer to 4.23.10 Precautions below).

Thymus disorders

People with a history of any thymus disorder, including myasthenia gravis, thymoma, thymectomy and DiGeorge syndrome, or thymic damage from chemoradiotherapy or graft-versus-host disease, should not be given the yellow fever vaccine due to the increased risk of yellow fever vaccine-associated viscerotropic disease\textsuperscript{38} (refer to 4.23.11 Adverse events below).
4.23.10 Precautions

Adults aged ≥60 years

The risk of severe adverse events following yellow fever vaccine is greater in those aged ≥60 years than in younger adults.\textsuperscript{39-43}

Adults ≥60 years of age should be given yellow fever vaccine only if they intend to travel to endemic countries (as recommended above) and they have been informed about the (albeit very low) risks of developing a severe complication.

HIV-infected persons

Yellow fever vaccine can be administered to HIV-infected persons who are at risk of yellow fever virus infection, providing they are not immunocompromised (refer to 3.3.3 Vaccination of immunocompromised persons). Studies of yellow fever vaccine in small numbers of HIV-infected participants suggest a reduced immune response, but vaccination is well tolerated\textsuperscript{14,15} (refer to 4.23.4 Vaccine above).

There are few studies of yellow fever vaccine in HIV-infected persons with CD4\textsuperscript{+} counts <200 per µL and a decision to vaccinate such persons where risk of yellow fever infection is unavoidable should be considered on a case-by-case basis.

4.23.11 Adverse events

Mild adverse events

Adverse events following yellow fever vaccine are generally mild. Vaccine recipients often report mild headaches, myalgia and low-grade fevers or other minor symptoms in the first 5 days after vaccination, which can last up to 2 weeks.\textsuperscript{44} In clinical trials in which symptoms are actively elicited, up to 25% of vaccine recipients report mild adverse events and up to 1% curtail regular activities.\textsuperscript{4,42,45}

Immediate hypersensitivity reactions

Immediate hypersensitivity reactions, including anaphylaxis, following yellow fever vaccine are very rare, with an incidence of less than 1 in 1 million, and occur principally in people with anaphylactic sensitivity to eggs.\textsuperscript{4,41,42} Although it has been suggested that an anaphylactic sensitivity to gelatin (added as a stabiliser to some yellow fever vaccines) may also precipitate anaphylaxis following vaccination,\textsuperscript{46} Stamaril does not contain gelatin.

Vaccine-associated neurotropic adverse events

Yellow fever vaccine-associated neurotropic disease (YF-AND) is a severe adverse event that is rarely fatal. YF-AND manifests as several distinct clinical syndromes, including meningoencephalitis (neurotropic disease), Guillain-Barré syndrome, acute disseminated encephalomyelitis and bulbar palsy.\textsuperscript{47,48} Between 1989 and March 2011, 113 cases of neurological adverse events following yellow fever vaccination were reported worldwide.\textsuperscript{4}

YF-AND is more likely to occur in very young infants and the elderly. Of 23 cases of meningoencephalitis reported between 1945 and 2001, 16 (70%) were infants <9 months of age with the majority <4 months of age. Recommendations made in the 1960s against immunisation of infants aged <6 months led to a reduction in the number of reports.\textsuperscript{49,50} Although YF-AND is rare in adults overall, the risk among adults is greatest in persons ≥60 years of age.\textsuperscript{39,41,51}

Vaccine-associated viscerotropic adverse events

Yellow fever vaccine-associated viscerotropic disease (YF-AVD), characterised by multi-organ system failure, is a recognised rare (3–4 cases per million doses of vaccine) but severe adverse event following yellow fever vaccination. YF-AVD mimics naturally acquired yellow fever disease, with the vaccine virus proliferating and disseminating throughout the host’s tissues.\textsuperscript{52}
Two risk factors have been identified for YF-AVD: older age and a history of thymus disease or thymectomy. A systematic review of YF-AVD among the elderly completed by the WHO found evidence to support an increased risk of YF-AVD among elderly travellers, though the risk among the elderly in endemic populations is undetermined. Four of the initial 27 reported cases of YF-AVD worldwide occurred in persons who had thymectomies performed for thymomas, a condition with a low prevalence in the general population.

A number of cases of YF-AVD have involved a history of autoimmune disease or diseases with potential autoimmune aetiology. However, in a number of these cases, the individual also had another known risk factor. More information is needed to inform whether there is a greater risk of YF-AVD in persons with autoimmune disease.

4.23.12 Public health management of yellow fever

Yellow fever is a notifiable and quarantinable disease in all states and territories in Australia. Further instructions about the public health management of yellow fever, including management of cases of yellow fever and their contacts, should be obtained from state/territory public health authorities (refer to Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control).

4.23.13 Variations from product information

The product information states that pregnancy is a contraindication to the yellow fever vaccine. The ATAGI recommends instead that pregnant women can be vaccinated where travel to an area with a risk of yellow fever virus transmission is unavoidable.

References

A full reference list is available on the electronic Handbook or website www.immunise.health.gov.au.


26. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Grading of recommendations, assessment, development, and evaluation
10th edition (update: August 2017)


29. Omilabu SA, Adejumo JO, Olaleye OD, Fagbami AH, Baba SS. Yellow fever haemagglutination-inhibiting, neutralising and IgM antibodies in vaccinated and unvaccinated residents of Ibadan, Nigeria. Comparative Immunology, Microbiology and Infectious Diseases 1990;13:95-100.


