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Yellow fever

Prevention in travellers

Background

Yellow fever is a mosquito borne flaviviral haemorrhagic fever endemic to parts of Africa and South America. One in seven patients develop severe, frequently fatal disease characterised by multi-organ involvement.

Objective

This article outlines the clinical features, epidemiology, prevention and vaccine recommendations for yellow fever in order to assist the general practitioner when providing travel medicine advice to patients.

Discussion

Travellers are at risk of yellow fever in endemic areas, especially in forested and rural regions and during urban outbreaks. In addition to antimosquito measures, it is important to prevent yellow fever by vaccinating where there is true risk, or where it is required by international health regulations. However, the vaccine is associated with rare but severe adverse reactions and the need for vaccination should be carefully evaluated.

Keywords: general practice; immunisation; yellow fever; travel



Yellow fever is a mosquito borne viral haemorrhagic fever caused by yellow fever virus – a single stranded ribonucleic acid virus of the genus flavivirus.^{1,2} It has an overall case fatality rate of up to 20%¹ and an estimated 200 000 cases of yellow fever, causing 30 000 deaths, occur worldwide each year in the endemic areas of Africa and South America.³ The vector, usually *Aedes aegypti*, is a domesticated mosquito, widespread in tropical areas.

Yellow fever can be difficult to diagnose as the early symptoms are nonspecific. It is a biphasic (sometimes considered triphasic) illness.^{4,5}

The first, 'acute' phase of intense viraemia is characterised by flu-like symptoms including fever, chills, prostration, myalgia, headache, nausea, vomiting and anorexia, starting 3–6 days after the bite of an infected mosquito.

Most patients improve after 3–4 days, but

after a few days of abatement of initial symptoms (which may be considered the second phase), 15% of patients enter a 'toxic phase' of viscerotropic complications (affecting liver, heart and kidneys) with increasing fever, jaundice, renal failure, thrombocytopenia, and coagulopathy. Fifty percent of patients who enter this phase die within 2 weeks; the remainder recover without organ damage.^{1–3} There is no specific treatment for yellow fever; management is supportive only.³

History

Yellow fever virus, identified by Max Theiler in the late 1920s, originated in Africa and spread to the western hemisphere during the era of slave trade. It is antigenically related to other group B arboviruses, which are named flaviviruses after the latin term *flavus*, meaning yellow. The first epidemic of yellow fever was reported in the Yucatan peninsula in 1648, followed by outbreaks in tropical America, the coastal cities of North America, and in Europe.⁶ Walter Reed and his colleagues, at the turn of last century, proved that *A. aegypti* mosquitoes were the primary mode of transmission.⁷ General William Gorgas then instituted an antimosquito campaign in Havana and eliminated the disease there in 1902, and 4 years later in Panama, allowing for completion of the Panama Canal. The discoveries that yellow fever is a zoonosis maintained by sylvatic mosquito species and nonhuman primates in the Amazon jungle, and that the virus is able to transmit vertically in mosquitoes, explained why further efforts towards eradication were unsuccessful. Tropical regions of Africa and the Americas, but not Asia, were found to have endemic virus transmission. Mass vaccination campaigns in South America and francophone Africa started in the 1940s, but the disease spread to Central America in the 1950s and epidemics occurred in Africa and the Americas in the 1960s. Another expansion of yellow fever activity occurred in Africa during the 1980s due to

amplification of the enzootic transmission cycle coupled with poor vaccine coverage.

In 1988, the World Health Organization and the Pan American Health Organization started to promote the inclusion of yellow fever vaccine in childhood vaccination schedules, with catch-up campaigns in 12 West African countries for those not covered.

Epidemiology

Yellow fever occurs in the tropical parts of Africa and Central and South America (Figure 1, 2) where the virus is enzootic in rainforest monkey species and certain canopy mosquitoes. The disease is significantly underreported.¹

Transmission can be vector borne (via the bite of an infected mosquito) or anthroponotic (human-to-vector-to-human), and occurs in three ways:^{1,2}

- sporadic human cases of sylvatic or jungle yellow fever can occur if persons enter forest areas, with transmission of the virus from monkeys via mosquitoes
- 'intermediate' small outbreaks occur in African savannah regions adjacent to rainforest areas, where *Aedes* mosquito species can again transfer the virus from monkeys to humans and then between humans (anthroponotic transmission)
- large 'urban' epidemics can occur in cities and rural areas of tropical Africa and Central/South America where *A. aegypti* species are endemic. In these situations a viraemic individual can infect local mosquitoes who then continue to transmit the virus from person-to-person. There is also potential for blood borne transmission during the viraemic phase.

Although *A. aegypti* species are found throughout much of tropical Asia and Oceania (including northern Queensland), yellow fever has never been reported in these regions.¹

Yellow fever has increased worldwide due to declining population immunity to infection, deforestation, urbanisation, population movements and climate change.³ In West Africa, five urban epidemics have occurred since 2001, including Côte d'Ivoire, Guinea, Senegal, and Burkina Faso.¹

Risk to travellers

At least six cases of yellow fever, all fatal, have been reported in unvaccinated travellers to Africa and South America since 1996.¹ Only one case,

acquired in West Africa, has been reported in a vaccinated traveller.²

Risk to travellers varies depending on itinerary, season, and use of effective mosquito avoidance measures. Travellers are at risk in all areas in which yellow fever is endemic; the risk increases with travel to jungle areas (Table 1).⁸ Risk in rural West Africa is higher between July to October, at the end of the rainy season, and at the start of the dry season (but risk is not absent at other times) (Figure 1). Risk in South America is greater during the rainy season (January to May) and highest in February/March, but urban epidemics can also occur at other times. Risk to travellers is lower than that in Africa;² the areas considered to be the highest risk are Bolivia, Brazil, Colombia, Ecuador and Peru (Figure 2).³

Approximate risk for an unvaccinated individual travelling for 2 weeks to an endemic area of West Africa is 50 per 100 000 of becoming ill, and 10 per 100 000 of death due to yellow fever. Risks in South America are 5 per 100 000 and 1 per 100 000 respectively (see Resources).^{2,9}

Prevention in travellers

Patients should stay indoors or under mosquito nets to avoid contributing to the transmission cycle.² Advice should be given regarding avoidance of epidemics and minimisation of high risk behaviour (eg. jungle visits). Personal protective measures are an important part of any travel medicine consultation where the traveller is heading to any region of mosquito borne disease. Mosquito avoidance includes the use of treated mosquito nets and screening of living and work areas (see Resources).^{1,2}

In high risk areas such as West African savannah regions, it is advisable where possible to spray indoor living spaces, including secluded spaces such as closets, with pyrethrin insecticides.¹⁰ Yellow fever mosquito vectors usually bite during the day.¹

Yellow fever vaccine

Stamaril is the live, attenuated yellow fever virus (17D-204 strain) freeze dried vaccine available in



Figure 1. Yellow fever endemic zones in Africa, 2009²



Figure 2. Yellow fever endemic zones in the Americas, 2009²

Australia. It is given as a single intramuscular or subcutaneous injection of 0.5 mL of reconstituted vaccine.^{8,11} Stamaril has an efficacy approaching 100% and is generally well tolerated. Protective immunity occurs within 1–2 weeks in 90–95% of people, and a single dose lasts for at least 10 years.^{1,4,8} Under international health regulations, revaccination is required every 10 years.¹

Contraindications

- Known anaphylactic sensitivity – anaphylaxis related to a previous dose or any of the vaccine components
- Anaphylaxis to eggs

- Age 9 months or less
- Altered immune status including symptomatic HIV or AIDS
- Thymus disorders including myasthenia gravis, thymoma, thymectomy and DiGeorge syndrome.¹

Although the vaccine product information and various other sources recommend giving intradermal test doses to individuals with a history of egg allergy^{2,10,12} (which in some cases may induce protective immunity even if the full dose is not given),¹² this practice is not recommended by the National Health and Medical Research Council.¹ In individuals whose immune status is altered by HIV infection, and their risk of exposure to yellow fever is high, it is possible to give 17D vaccine if they are asymptomatic and CD4 cell counts are >200/mm³.^{2,10} Immunisation should be followed by measurement of the neutralising antibody response 2–4 weeks later as seroconversion rates and vaccine effectiveness may be reduced.^{1,2,10,13} successful antiretroviral therapy may improve vaccine response.¹³ A medical waiver should be considered for vaccine eligible HIV infected travellers who will not be at true risk and are considering vaccination only to satisfy international health regulations.^{2,10} Yellow fever vaccine may also be given to individuals taking prednisolone orally at doses of 10 mg/day (or 20 mg/day according to Centers for Disease Control) or less, or are using intranasal

corticosteroids, are on systemic corticosteroid therapy for 2 weeks or less, or are receiving intra-articular, bursal or tendon corticosteroid injections.^{2,10} Specialist advice should be sought where more detailed and individualised information is required.

Vaccine precautions

Age

Adults aged more than 60 years should be given yellow fever vaccine only if they intend to travel to endemic countries and have been informed about the risks of developing a severe complication.

Pregnancy

As YF17D is a live vaccine, it should be avoided in pregnancy unless there is a risk of exposure to the virus. Pregnant women should be advised against travelling to endemic areas. Those who insist on going ahead with a risky itinerary against medical advice, especially to West Africa or outside urban areas of any other endemic country, should receive yellow fever vaccine. Many pregnant women have received this vaccine with no evidence of adverse outcomes.¹ Congenital infection of the fetus occurs in approximately 1–2% but has not been associated with fetal abnormalities,¹⁰ although a slightly increased risk has been noted for minor, mostly skin, malformations after vaccination in early pregnancy.² There are no grounds for termination if the vaccine is given in the first trimester.¹ As the efficacy data for immunisation during pregnancy is conflicting, it is worthwhile considering measuring antibody titres after immunisation.¹⁴ A medical waiver should be given to pregnant women where the risk of exposure is considered less than the risk of vaccination.²

Breastfeeding

It is not known whether the yellow fever vaccine is excreted in breast milk. One suspected case of yellow fever vaccine associated neurotropic disease (YEL-AND) was reported in an exclusively breastfed baby 1 month of age after maternal vaccination.¹⁵ Breastfeeding women should avoid vaccination unless high risk travel is unavoidable.²

Administration of other vaccines on the same day

Other live virus vaccines such as measles-mumps-rubella should be administered on the same day

as yellow fever vaccine, or separated by a 4 week interval. Other travel related vaccines may be given on the same day or at any time before or after the yellow fever vaccine.¹

Adverse events

Most adverse events occur after primary vaccination.^{9,10} Up to 25% of patients experience mild side effects including myalgia, headache, low grade fever or discomfort at the injection site.^{8,9,16} Adults over 60 years of age are at increased risk of rare and severe systemic adverse events.

Severe adverse events

Immediate hypersensitivity reactions including urticarial rash and/or wheeze are uncommon. Anaphylaxis occurs in 1.8 cases per 100 000 vaccines administered.²

Yellow fever vaccine associated neurotropic disease includes different neurological syndromes including meningoencephalitis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, bulbar palsy and Bell palsy. In the past it occurred mainly in infants as encephalitis,¹⁰ leading to a change in vaccine recommendations to exclude infants <9 months of age (or <6 months of age in an epidemic situation).^{1,2} The onset ranges from 3–28 days postvaccination, usually in first time vaccinees. The incidence is 0.8 per 100 000 doses and is higher in persons aged 60 years or more (1.6 in 100 000 in the 60–69 years age group and 2.3 per 100 000 in those aged 70 years or more).² Where YEL-AND has occurred in adults, the recovery has usually been rapid and complete.¹⁶

Yellow fever vaccine associated viscerotropic disease (YEL-AVD) – multi-organ failure – has resulted in deaths, mostly in elderly persons. Patients usually present 2–5 days following vaccination. The illness is similar to fulminant yellow fever. Risk factors include age >60 years and a history of thymus disease or thymectomy.^{1,2,9,10,16–18} It is likely that these events are underreported; the risk generally quoted is 1 in 200 000–400 000,^{6,10,17} but rises to 1 per 100 000 doses in the 60–69 years age group and 2.3 per 100 000 doses in persons aged 70 years or more.² A cluster of cases recently occurred in Peru during a postdisaster yellow fever vaccination campaign.¹⁸ It has been recommended that patients who present with an undiagnosed febrile illness within 10 days of vaccination should be investigated, and

Table 1. Yellow fever endemic countries

West African countries

Benin, Burkina Faso, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Nigeria, Senegal, Sierra Leone, Togo

Other African countries with risk of yellow fever transmission

Angola, Burundi, Cameroon, Central African Republic, Chad, Republic of the Congo, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Kenya, Niger, Rwanda, Sao Tome and Principe, Somalia, Sudan, Tanzania, Uganda

Central and South American countries with risk of yellow fever transmission

Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Panama, Paraguay, Peru, Suriname, Trinidad and Tobago, Venezuela

that those with elevated liver enzymes should be admitted to hospital for observation.¹⁰

Recommendations for travellers

The risk to unvaccinated individuals who visit countries where there may be yellow fever transmission is far greater than the risk of a vaccine related adverse event, and it remains important for all travellers to be vaccinated. Nonetheless, yellow fever vaccination should not be prescribed for individuals who are not at risk of infection, based on an accurate assessment of the travel itinerary. Yellow fever vaccination should be encouraged as a key prevention strategy, but it is important to screen travel itineraries, particularly of older travellers, and carefully evaluate the potential risk of systemic illness after yellow fever vaccination.¹⁷

The yellow fever vaccine is recommended for the following travellers:¹⁷

- those ≥9 months of age travelling or living in any country in West Africa, regardless of itinerary within that country
- those ≥9 months of age travelling or living outside urban areas of all other yellow fever endemic countries.

Mandatory vaccination requirements

A number of countries have specific mandatory vaccination requirements for travellers entering that country. Detailed country-by-country vaccination requirements are available online from the Centres for Disease and Control website (see *Resources*).² The absence of a mandatory requirement does not imply the absence of risk. Conversely, *A. aegypti* and other yellow fever vector species exist in many nonendemic countries which have vaccination requirements to aid in the prevention of yellow fever transmission; this includes Australia, where *A. aegypti* exist in northern Queensland.¹ Travellers on overnight transit through a yellow fever endemic country may be required to show proof of immunisation upon entering a nonendemic country; this should be kept in mind while planning a travel itinerary.

Yellow fever vaccination certification

Vaccination must take place at an approved vaccination centre and recorded in an International Certificate of Vaccination or Prophylaxis (ICVP)

against yellow fever and must include the vaccinee's name and signature (or that of parent/guardian) and the signature of the person approved by the relevant health authority. The official stamp provided by the state/territory health authority must be used. The certificate becomes valid 10 days after vaccination (or from the day of the vaccine if it is a booster dose)² and stays valid for 10 years.¹ The format for ICVP forms, conforming to the revised International Health Regulations 2005, is available online or forms can be purchased from the World Health Organization (see *Resources*).

A formal waiver letter (as discussed) for travellers with a true vaccine contraindication can be written by their doctor on practice letterhead, signed and dated, and clearly stating the reason for withholding the vaccine.¹ A waiver does not guarantee its acceptance by the country of destination, so travellers may consider obtaining additional advice and/or documentation from the embassy or consulate to attach to the completed medical contraindication to vaccination section of the ICVP.²

Conclusion

The risk to travellers of contracting yellow fever has to be balanced carefully against the small but serious risks of vaccination. A knowledge of the traveller's itinerary and activities, risk factors for adverse effects of the vaccine, and access to up-to-date epidemiological information and international health regulations regarding yellow fever are important in order to advise and vaccinate travellers appropriately.

Resources

- Mosquito avoidance information: <http://www.wnc.cdc.gov/travel/yellowbook/2010/chapter-2/protection-against-mosquitoes-ticks-insects-arthropods.aspx>
- Yellow fever outbreak information: www.who.int/csr/don/archive/disease/yellow_fever/en/index.html
- Country-by-country entry requirements and recommendations for yellow fever vaccination: <http://www.wnc.cdc.gov/travel/yellowbook/2010/chapter-2/yellow-fever-vaccine-requirements-and-recommendations.aspx>
- ICVP forms: www.who.int/csr/ihr/ivc_no_logo.pdf

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