

Yellow Fever

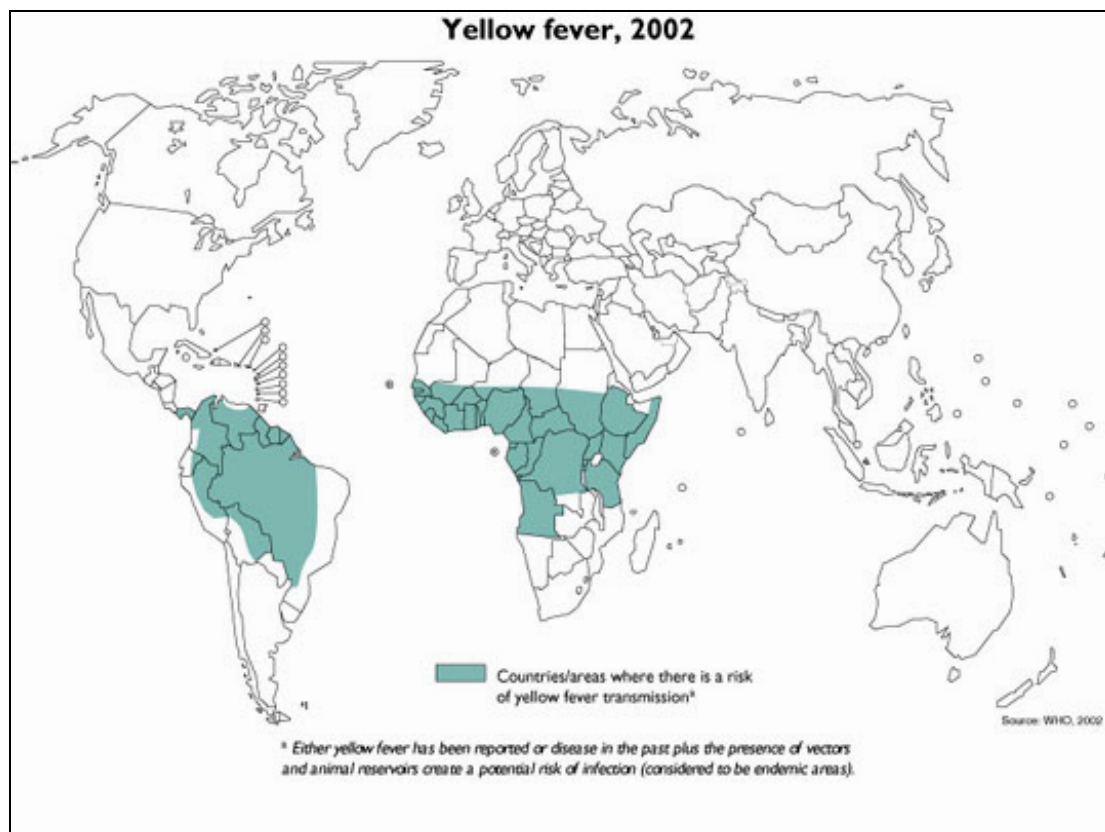
Introduction

Yellow fever (YF) virus is an arthropod borne virus of the Flaviviridae family within the genus flavivirus. Other flaviviruses include dengue fever and Japanese encephalitis viruses. YF is considered to be one of the most lethal viral diseases. The endemic zones for the disease are in tropical regions of Africa and South America.

Epidemiology

(Data from the Travel Health Surveillance Section of the Health Protection Agency, Communicable disease Surveillance Centre)

Global epidemiology



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YF is endemic in tropical parts of Africa and South America. Endemic regions include countries (or areas within countries) where there is the potential for human infection because of the presence of YF virus in mosquitoes and non-human primates.

To date YF has not appeared in Asia or the Pacific region. The World Health Organization (WHO) estimates that there are approximately 200,000 cases of YF every

year with 30,000 deaths. Under the current International Health Regulations (1) cases of YF should be reported to the WHO. Countries that are reporting human cases are termed infected countries. However, yellow fever is under reported, especially in Africa where the disease is most prevalent. In addition, infected areas could be more widespread than those officially reported as case rates may fall below the level of detection by surveillance, or surveillance may be incomplete. As an example of underreporting, in 1999, only 208 cases (including 101 deaths) of YF were officially notified to the WHO and all but one of the reports originated from the Americas.

Outbreaks of Yellow Fever

In recent years, outbreaks of YF have been reported to the WHO most commonly from West Africa (<http://www.who.int/disease-outbreak-news/disease/A95.htm>). Since the year 2000 there have been outbreaks in Liberia, Côte D'Ivoire, Nigeria, Guinea, Peru and Brazil. In 2002, an outbreak reported in Senegal involved 60 cases including 11 deaths; most cases occurred in the central area north of The Gambia but one case occurred in the capital Dakar. In 2003, there have been five outbreaks reported; three in West Africa (Guinea, Sierra Leone and Burkina Faso) and one in Sudan where there were 178 cases and 27 deaths. In February 2003, an outbreak of sylvatic YF was reported in Brazil in which there were 24 cases and five deaths all reported from Minas Gerais state.

Yellow Fever in UK Travellers

Since 1982 there have been two Statutory Notifications of YF in England and Wales, but no laboratory reports to CDSC. Statutory Notifications are made on the grounds of clinical suspicion and/or diagnosis therefore notified cases may not have been laboratory confirmed or reported through the laboratory network. The last known case occurring in the UK was in a laboratory worker who contracted the disease whilst working with the yellow fever virus at the Hospital for Tropical Diseases in London (2)

There have been, however, other cases in European and American travellers. In 1996 two tourists died from YF following trips to the Amazon Basin in Brazil (3,4) A further two travellers died in 1999 after contracting the virus in Venezuela and Cote d'Ivoire, (5,6) and in 2001 a traveller died in a Belgian hospital after contracting YF whilst on holiday near the Gambia/Senegal border (7). In 2002, an American died of YF after returning from a fishing trip on the Amazon near Manaus, Brazil (8).

Risk for Travellers

The risk of contracting YF is determined by the following factors:

- Travel destination
- Intensity of YF transmission in area to be visited
- Season of travel
- Duration of travel
- Activities allowing exposure to mosquitoes
- Immunisation status

Although ongoing cases and outbreaks of YF are occurring in Africa and South America, the disease is preventable by vaccination and remains a very rare cause of illness in travellers. In recent years there have been six recorded deaths from YF in non-vaccinated travellers.

Transmission

Jungle primates and humans are the vertebrate hosts for the YF virus. The female *Aedes sp.* or *Haemogogus sp.* (South America only) mosquito is the vector and a bite from an infected female of these species may transmit the virus.

Transmission of yellow fever occurs in two main cycles:

- **Sylvatic (jungle):** occurring in tropical rainforests of Africa and South America. The transmission cycle occurs between monkeys and wild mosquitoes (i.e. those breeding in the jungle). Humans may become infected when they live or work in areas where this cycle occurs.
- **Urban:** following infection during the sylvatic cycle, humans import the virus to urban areas where there is a high population density. Virus transmission occurs from human to human where the domesticated mosquito (i.e. those that breed around houses) is present (exclusively *Aedes aegypti*).

The *Aedes* mosquito is active during daylight hours and bites from dawn to dusk. Once infected with the virus, the mosquito remains infectious for life (2-3 months). Whilst the mosquito is killed by extremes of heat and cold, the virus can survive from season to season in mosquito eggs. This makes eradication of the disease difficult.

Signs and symptoms

Yellow fever varies in severity. The infection has an incubation period of 3 to 6 days. Initial symptoms include myalgia, pyrexia, headache, anorexia, nausea and vomiting. Despite the high fever, the pulse is often disproportionately slow. In many patients there will be improvement in symptoms and gradual recovery occurring three to four days

after the onset of symptoms. However, within 24 hours of an apparent recovery, 15% to 25% of patients progress to a more serious illness. This takes the form of an acute haemorrhagic fever, in which there may be bleeding from the mouth, eyes, ears and stomach, pronounced jaundice (from which the disease gets its name) and renal damage. The patient develops shock and there is deterioration of major organ function. Twenty to 50% of patients who develop this form of the disease die within 7-10 days after the onset⁹.

Infection confers lifelong immunity in those who recover.

Treatment

There is no specific antiviral treatment. Supportive nursing care and symptomatic management are the standard.

Prevention

There are two methods to prevent YF: mosquito bite avoidance and control, and immunisation. A highly effective live attenuated yellow fever vaccine has been available for more than 50 years. In general, vaccination is recommended for all persons visiting countries where there is a risk of YF virus transmission. These usually are countries that lie in the endemic zones for YF.

Persons who insist on travelling to countries where YF is a risk without the benefit of vaccination, should be advised of the risk of contracting YF and the potential for quarantine, depending on certificate requirements. Meticulous mosquito bite avoidance should be advised.

International Health Regulations

The International Health Regulations (1) adopted by the World Health Organisation (WHO) were formulated to help prevent the international spread of disease, and in the context of international travel, to do so with the minimum of inconvenience to the traveller. The Regulations were designed primarily as a public health measure for the receiving country rather than for the protection of the individual. Yellow fever is now the only disease for which an International Certificate of Vaccination may be required for entry into a country.

A proportion of mandatory vaccination against yellow fever is carried out with the aim of preventing yellow fever virus from being imported into vulnerable or receptive countries. These are countries where yellow fever does not occur but where the mosquito vector and often the non-human primate hosts are present. Importation of the virus could lead to YF in the local population. In these cases, vaccination may be an entry requirement for all travellers (occasionally including airport transit) arriving from countries, where there is a risk of yellow fever transmission. Failure to provide a valid certificate to the port health authorities could, in some circumstances, result in a traveller being quarantined or possibly immunised or denied entry.

If yellow fever vaccination is contraindicated for medical reasons (including infants < 9 months of age), a medical waiver letter/certificate of exemption should be issued if appropriate.

Information on country requirements for yellow fever is published annually by the WHO in *International Travel and Health*. Information regarding becoming a Yellow Fever Vaccination Centre is on the NaTHNaC website.

The absence of a requirement for vaccination (refer to WHO International Travel and Health) does not imply that there is no risk of yellow fever in the country, and yellow fever immunisation may be recommended for the protection of the individual traveller (see Health Information for Overseas Travel) for yellow fever recommendations for individual countries).

Yellow Fever Vaccine Information

Indications

Yellow fever (YF) vaccination may be recommended for travel to all countries in the endemic zones whether or not an international certificate is required.

- **'Endemic' regions** include countries (or areas within countries) where there is the potential for human infection because of the presence of YF virus in mosquitoes and non-human primates. The potential to introduce YF into humans and to urban settings exists in endemic countries. Because of the possibility of acquiring disease in endemic countries, vaccination against YF may be recommended for travellers, particularly those who visit rural areas. In some cases vaccination may be mandatory.
- **'Infected' countries** are those that are reporting human cases of YF to the World Health Organisation (WHO). Countries infected with YF are listed in the Weekly Epidemiological Record. Vaccination is recommended and may be required for visitors to infected areas. Because of under reporting, infected areas may be more widespread than those that are formally designated as infected by the WHO.

Availability

There are currently two yellow fever vaccines licensed for use in the United Kingdom. These use the 17D strain of yellow fever virus.

Vaccine	Manufacturer/ Distributor	Schedule	Length of protection	Age range
Arilvax	Chiron	1 dose	10 years	Minimum age 9 months. Seek medical advice for infants 6-9 months who are travelling to high risk areas
Stamaril	Aventis Pasteur	1 dose		

We strongly advise that the SPC is consulted prior to the administration of any vaccine.

The vaccine induces a rapid immune response with 90% of recipients achieving protective levels of antibody within 10 days. Immunity following vaccination has been shown to be long lasting and possibly life long. However, International Health Regulations require re-vaccination at 10-year intervals if indicated, in order to retain a valid certificate and prevent the importation of yellow fever virus into susceptible countries.

Contraindications

- Children under 9 months of age
- Febrile illness
- Immunocompromised hosts
- Pregnancy (unless the risk of disease outweighs the theoretical risk of vaccination)
- Anaphylaxis to egg protein
- Allergy to any component of vaccine
- Thymus disorder, including myasthenia gravis, thymoma, thymectomy, and DiGeorge syndrome. (10)

Adverse Events

The 17D strain virus yellow fever vaccine has been in use for more than 50 years and has an excellent safety profile. It has been estimated that 300-400 million doses of the vaccine have been administered worldwide (11). Reactions to YF vaccine are usually mild and short lived. They include myalgia, headache, low-grade fever, and typically occur during the first 5-10 days post vaccination.

Serious adverse events are rare but have been reported and fall into three main categories: hypersensitivity reactions, vaccine-associated neurotropic disease (VAND) and vaccine-associated viscerotropic disease (VAVD).

Hypersensitivity reactions

The vaccine is propagated in chick embryos. Vaccine stabilizers include beef gelatine and sorbitol. Anaphylaxis and urticaria as a result of sensitivity to either egg or other vaccine components, occurs at an incidence between 1:130,000 and 1:250,000 (12).

Vaccine-Associated Neurotropic Disease (VAND)

VAND manifests as post-vaccine encephalitis with fever, headache, cognitive impairment and CSF pleocytosis. There have been at least 26 cases worldwide of encephalitis (temporally associated with or confirmed to be caused by 17D strain vaccine) reported in the scientific literature since 1945. Sixteen cases were infants under 9 months of age (13). Infants below 6 months of age seem to be more susceptible to post-vaccine encephalitis and for this reason vaccine should not be given in this age group.

Reports since the mid 1990's have described several cases of VAND in adult recipients of YF vaccine (14). The risk is about 6 cases per million doses of YF vaccine and is higher for vaccine recipients over the age of 60 years.

Vaccine-Associated Viscerotropic Disease (VAVD)

VAVD manifests as fever, jaundice and multiple-organ system failure following YF vaccination. The syndrome has only been recently recognised after the first 7 cases were reported from 1996 to 2001 (15). To date there have been 7 confirmed cases and up to 11 suspected or probable cases of VAVD worldwide (11). All cases have occurred following the first YF vaccination (11).

It is not known if underlying host factors (genetic or acquired) or pre-existing clinical conditions contribute to the course or outcome of yellow fever VAVD.

Estimated reported incidence of VAVD in US citizens was found to be 1 per 200,000 to 300,000 doses distributed, however, it is possible that the syndrome has been under-reported (11). The frequency is three-to four-fold higher in persons over the age of 60 years. There have been no reports of VAVD in the United Kingdom.

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