Yellow Fever

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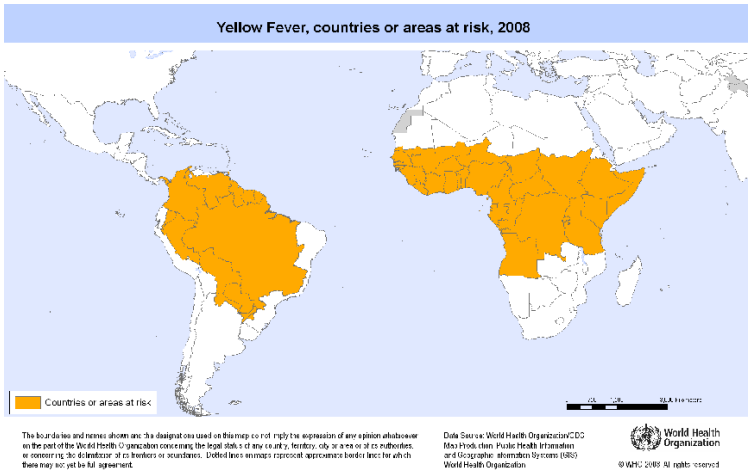
Yellow fever (YF) is a systemic viral disease transmitted by mosquito.

The disease only occurs in tropical areas of South America, Panama in Central America, Trinidad in the Caribbean and sub Saharan Africa.



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Countries with a risk of YF are required to report cases to the World Health Organization (WHO). In 2007, 11 cases were officially reported from five countries in Africa. In South America, 48 cases were officially reported from four countries. However, the disease is greatly underreported and the true number of cases is difficult to estimate. It has been suggested that for every symptomatic case, there are seven asymptomatic cases.

Unvaccinated travellers are at risk when visiting areas where the disease is known to be transmitted. Globally since 1979, there have been 10 reported cases of YF in unvaccinated travellers; nine of those cases died of the disease.

Epidemiology

YF is a vaccine preventable mosquito borne disease. YF virus (YFV) is a member of the family *Flaviviridae*, genus *Flavivirus.*

YFV is transmitted by an infected female mosquito as she takes a blood meal, necessary to complete the reproductive cycle, from a monkey or human. The female can transmit virus to her progeny. She lays eggs, which although laid in fresh water, can survive long periods of desiccation and hatch when conditions are right. The main vector is the *Aedes* mosquito or closely related species, which bite during the day. Monkeys are the main reservoir of infection.

There are three transmission cycles:

Jungle / Sylvatic: the virus is transmitted from mosquito to monkey in the forest. Humans become infected during incursions into the jungle environment (e.g. for work or leisure).

Urban: the virus is first introduced into the urban environment by an infected (viraemic) human. Urban mosquitoes (*Aedes aegypti*) become infected after taking a blood meal from an infected individual and begin a transmission cycle between humans and mosquito.

Savannah (Africa only): the virus is transmitted between mosquito, monkeys and humans who live in close proximity at the forest edge.

Transmission occurs year round, particularly in the jungle environment, where there is regular precipitation. Transmission risk is highest in the urban environment during and just after the rainy seasons.

Incubation period and clinical features

Following an infective mosquito bite, the incubation period in a human is three to six days. Infection can be asymptomatic or present as a non-specific febrile illness with symptoms that include headache and myalgia. More severe symptoms may be present including photophobia, anorexia, irritability, epigastric tenderness and hepatomegaly. After five to 10 days of illness, symptoms begin to improve, however some cases progress after a short period of remission, to a severe illness with jaundice, hypotension and multi-organ failure that is frequently fatal.

The onset of symptoms is abrupt and the viraemic phase lasts between three to four days. During this time, the individual is infectious to the mosquito and should be nursed in screened accommodation and under a

net in countries where onward mosquito transmission is a risk. In the UK, cases of suspected imported yellow fever are very rare. Guidelines relating to the management and control of haemorrhagic fevers in the UK are available from the Health Protection Agency. There is no specific anti-viral treatment for YF. Intensive supportive care is required for severe cases. There is a case fatality rate (CFR) of about 50% in those with severe illness.

It would be rare to see a traveller returning to the United Kingdom with YF. Malaria is more likely and can be rapidly life threatening. Any returned traveller with a fever should be evaluated urgently by a tropical or infectious disease expert.

Prevention

Vector control.

The urban transmission of YF in risk areas can be reduced by vector control using larvacides and insecticides to interrupt the mosquito breeding cycle. This approach is impractical in the jungle environment.

Insect bite avoidance.

All travellers to YF risk areas should be advised to use insect bite avoidance measures, mindful that the disease is transmitted by mosquitoes that are most active during daylight hours. Insect repellents containing N, N-diethylmetatoluamide (DEET) are the most effective.

Yellow fever vaccination. Vaccination is an effective method of preventing YF for children aged over nine months of age and adults who live in or are planning to visit risk areas, and for individuals who work with the live virus.

The vaccine available in the UK (Stamaril) is live and contains the 17D (204) strain of the virus, attenuated by serial passage through hens egg embryos. It contains no antibiotics or preservatives. It is supplied in a lyophilised preparation with a diluent and must be reconstituted immediately before use. The dose (0.5 ml of reconstituted vaccine) is the same for all age groups and the vaccine is given either subcutaneously or intramuscularly.

Contraindications

- Children aged under six months of age: there is an increased risk of vaccine associated encephalitis.
- Anaphylactic reaction to a previous dose of yellow fever vaccine or to any components of the vaccine.
- Confirmed anaphylactic reaction to eggs or chicken.
- Individuals with a thymus disorder including thymoma, thymectomy, myasthenia gravis and Di George syndrome: due to the increased risk of vaccine associated viscerotropic disease (see below)
- Individuals who are immunocompromised by a disease process, or current or recent immunosuppressive treatment.

Precautions

- Pregnancy: the safety of YF vaccine in pregnancy has not been evaluated. Limited studies of women inadvertently vaccinated in early pregnancy do not indicate a higher risk of miscarriage or foetal malformation; there is limited evidence that the virus can be transmitted transplacentally. If travel is unavoidable the decision to administer YF vaccine during pregnancy should be made after consideration of the risk of YF at the destination taking into consideration any evidence of previous vaccination and the informed choice of the traveller. Expert opinion should be sought.

- Breast feeding: the safety of YF vaccine administered during breastfeeding has not been evaluated. It is known that similar viruses can be excreted in breast milk, and caution should therefore be advised. YF vaccine can be offered to breastfeeding women if travel to a YF risk area is unavoidable.

- Over 60 years of age: there is an increased risk of serious systemic adverse events in individuals aged 60 years or older who are receiving the vaccine for the first time.

- Infants aged six to nine months of age: YF vaccine is recommended for infants at risk from nine months of age. However, the vaccine can be considered for infants aged from six months of age if the risk of YF is felt to be unavoidable. Expert opinion should be sought.

Following first time vaccination, neutralizing antibody to YF virus is present in 90% of individuals at 10 days and in about 99% of people at 30 days. The vaccine should be given at least 10 days before visiting a risk area in order that protection can be achieved. In addition, International Health Regulations (IHR (2005)) stipulate that an International Certificate of Vaccination or Prophylaxis (ICVP), required by some port authorities, is only considered valid 10 days after vaccination.

YF Vaccine-assocaited adverse events

Around 500 million doses of YF vaccine have been administered during the last sixty years and the vaccine has a good safety record. However, during the last decade two serious vaccine associated adverse event syndromes have been identified, Yellow Fever Vaccine-Associated Neurologic Disease (YEL-AND) and Yellow Fever Vaccine-Associated Viscerotropic Disease (YEL-AVD).YEL-AND. Post-vaccine encephalitis has been recognised as a rare event since the early use of 17D vaccine, particularly in infants aged under 6 months. Following the recommendation that YF vaccine should be restricted to children aged

over 6 months, there has been a reduction in the incidence of post-vaccine encephalitis in children. However, since 2001, a new pattern of neurologic adverse events affecting all age groups has been recognised and termed YEL-AND. The clinical presentation of neurologic events begins four to 23 days following receipt of vaccine, with fever and headache that may progress to encephalitis, demyelination, or Guillain Barré syndrome. Most patients will completely recover. All cases have occurred in primary vaccinees with no underlying YF immunity.YEL-AVD. YEL-AVD is a syndrome of fever and multi-organ failure that resembles severe YF disease. Two to eight days following vaccination, patients develop fever, malaise, headache, and myalgias that progress to hepatitis, hypotension, and multi-organ failure. Death has occurred in about 60% of reported cases. As with neurologic disease, all cases have occurred in primary vaccinees.

The rate of YEL-AND and YEL-AVD is estimated to be about five cases per million doses. For individuals who are aged 60 years and older, the risk of YEL-AND and YEL-AVD increases to about 25 cases per million doses.

International Health Regulations (2005)

The current IHR (2005) were adopted by the World Health Assembly in 2005 and came into effect in 2007. They were formulated to help prevent the international spread of disease. IHR (2005) are primarily a public health measure for the receiving country rather than for the protection of the individual. Currently YF is the only disease for which an ICVP may be required for entry into a country. The ICVP is used to record YF vaccination.

A proportion of mandatory vaccination against YF is carried out with the aim of preventing YF virus from being imported into vulnerable countries. These are countries where YF 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 YF transmission. Where YF vaccine is required under IHR (2005), failure to provide a valid ICVP to the port health authorities could result in a traveller being quarantined, immunised, or denied entry.

Under IHR (2005) YF vaccine can only be administered at designated Yellow Fever Vaccination Centres (YFVCs). In England, Wales and Northern Ireland YFVCs are designated by the National Travel Health Network and Centre (NaTHNaC). In Scotland YFVCs are designated by Health Protection Scotland (HPS).

Further information

NaTHNaC Health Information Sheet on Yellow Fever

http://www.nathnac.org/pro/factsheets/yellow.htm