

June 2009

## Yellow Fever

### Introduction

Yellow fever (YF) virus is an arthropod borne virus of the *Flaviviridae* family. Other flaviviruses include dengue and Japanese encephalitis viruses. YF is one of the most lethal viral diseases. The areas at risk for transmission of YF are in tropical regions of Africa and South America. Vaccination against YF is available and should be recorded in an International Certificate of Vaccination or Prophylaxis.

### Epidemiology

#### Global epidemiology

YF is a risk in tropical parts of Africa and South America. Areas with a risk of YF transmission are countries (or areas within countries) where infection is occurring in humans or primates and there is a competent mosquito vector (*Aedes* spp.). The World Health Organization (WHO) has estimated that as many as 200,000 cases of YF occur each year with 30,000 deaths (2002 estimate) [1]. Underreporting of YF infection is evident, as the number of annual confirmed cases reported to the WHO Between 2002 and 2006 were 672, 152, 588, 356, and 225 respectively [2]. Human cases often occur below the level of surveillance detection.

In consultation with the WHO and the Pan American Health Organization (PAHO), the US Centers for Disease Control and Prevention (CDC) have defined the areas at risk for YF transmission as illustrated in the maps below [3]. The dynamic nature of this disease has resulted in the identification of additional risk areas and changes to these maps. Updates to areas of YF risk can be found on the [NaTHNaC Country Information Pages](#).

#### Areas with Risk of Yellow Fever Transmission

##### Africa



## America



These maps are reproduced with acknowledgement to the US Centers for Disease Control and Prevention.

### Outbreaks of yellow fever

Between 2005 and July 2008, outbreaks of YF were reported in Burkina Faso, Central African Republic, Côte d'Ivoire, Guinea, Liberia, Mali, Senegal, Sudan, and Togo in Africa, and in Argentina, Brazil, Paraguay, and Peru in South America [4-12]. Reporting systems and the level of information that is sent to the WHO differs between countries and reported case numbers and outbreaks may not always accurately represent YF activity.

In January 2008, new outbreaks of YF occurred in Brazil, Paraguay, and Argentina [10,11]. These outbreaks led to changes to the YF vaccination recommendations for the countries involved (please see [NaTHNaC Country Information Pages](#)) [12]. The YF outbreak in Paraguay was the first recorded outbreak in the country since 1974.

Further information on recent outbreaks of YF can be found in the [Outbreak Surveillance Database](#) and the [Clinical Updates pages](#).

### Epidemiology of yellow fever in UK travellers

There were four statutory notifications of YF in England and Wales between 1993 and 2005 [13]. Statutory notifications are made on clinical criteria rather than laboratory confirmation. None of these notified cases had YF confirmed by laboratory testing. The last confirmed case that occurred in the UK, was a laboratory

worker who contracted YF while working with the YF virus at the Hospital for Tropical Diseases in London in 1930 [14].

## 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. There have been only six recorded deaths from YF in non-vaccinated European and American travellers between 1996 and 2007. In 1996, two tourists died from YF following trips to the Amazon Basin in Brazil [15,16]. A further two travellers died in 1999 after contracting the virus in Venezuela and Côte d'Ivoire [17,18], and in 2001, a traveller died in a Belgian hospital after contracting YF whilst on holiday near the Gambia/Senegal border [19]. In 2002, an American died of YF after returning from a fishing trip on the Amazon near Manaus, Brazil [20]. None of these travellers were vaccinated against YF.

## Transmission

Jungle primates and humans are the vertebrate hosts for the YF virus. The virus is transmitted via the bite of infected *Aedes* spp. or *Haemogogus* spp. (South America only) mosquitoes. Only females of these mosquito species transmit the virus.

Transmission of YF occurs in two main cycles:

- Sylvatic (jungle): occurring in tropical rainforests of Africa and South America. The transmission cycle occurs between monkeys and jungle breeding mosquitoes. Humans can become infected when they live or work in areas where this cycle occurs.
- Urban: following infection during the sylvatic cycle, infected humans can introduce the virus to urban areas where there is a high population density. Virus transmission occurs between humans in areas where the domesticated mosquito vector (i.e. those that breed around human habitation) 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 (two to three months). Although 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. *Haemagogous* spp. mosquitoes are also daytime biters.

## Signs and symptoms

YF varies in severity. The infection has an incubation period of three to six days. Initial symptoms include myalgia, pyrexia, headache, anorexia, nausea, and vomiting. 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; 20% to 50% of patients who develop this form of the disease do not survive [21].

Infection confers lifelong immunity in those who recover.

## Treatment

There is no specific antiviral treatment. Intensive 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 [YF 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. Travel to areas of risk without vaccination is not recommended. Persons who travel to countries where YF is a risk, without the benefit of vaccination, should be advised of both the risk of contracting YF and the potential for quarantine at the port of entry, depending on the requirements for YF vaccination. They should also practice meticulous mosquito [bite avoidance](#).

## International Health Regulations (IHR (2005))

The current IHR (2005) [22] which were revised and adopted by the World Health Assembly in 2005, were formulated to help prevent the international spread of disease, and in the context of international travel, do so with minimum disruption to trade and travel. The IHRs were designed primarily as 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 International Certificate of Vaccination or Prophylaxis (ICVP) may be required for entry into a country. The ICVP is used to record YF vaccination. In the future, proof of protection against other diseases could be required depending upon global health events.

A proportion of mandatory vaccination against YF is carried out with the aim of preventing YF virus from being imported into vulnerable or receptive 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. When 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.

If YF vaccination is contraindicated for medical reasons (including infants <9 months of age), a medical letter of exemption from vaccination can be issued.

Information on country requirements for YF is published annually by the WHO in [International Travel and Health](#) and can be found on the [NaTHNaC Country Information Pages](#).

Information regarding becoming a Yellow Fever Vaccination Centre is on the [NaTHNaC website](#).

*The absence of a requirement for YF vaccination does not necessarily mean that there is no risk of YF in the country, and YF immunisation may still be recommended for the protection of the individual traveller. Please review the requirements and recommendations for YF vaccine on the [NaTHNaC Country Information Pages](#).*

## Vaccine

### Indication for use of vaccine

- ◆ Yellow fever vaccine is indicated for susceptible adults and children aged nine months or older who require primary immunisation or booster vaccination against YF for personal protection, in order to comply with IHR (2005), or both (the requirement for vaccination against YF is not always related to the risk of exposure to disease)
- ◆ Laboratory workers handling infective material

A careful assessment that balances the risk of disease and any requirements for vaccination with the age and health status of traveller, needs to be performed prior to YF vaccination.

A model [Patient Group Direction](#) is available to registered UK Yellow Fever Vaccination Centres (login required) or on request by email to [nathnac@uclh.nhs.uk](mailto:nathnac@uclh.nhs.uk)

### Availability

There is currently one licensed YF vaccine in the UK. This contains an attenuated strain of the 17D strain of YF virus that protects against all strains of YF virus.

The Summary of Product Characteristics (SPC) for the vaccine should be consulted for specific information relating to the product.

Vaccine	Manufacturer/ Distributor	Schedule	Length of protection	Age range
Stamaril	Sanofi Pasteur MSD	1 dose	10 years	Minimum age 9 months. Seek medical advice for infants 6-8 months who are travelling to high risk areas

The vaccine induces a rapid immune response with 90% of recipients achieving protective levels of antibody within ten days. Immunity following vaccination has been shown to be long lasting and possibly life long. However, IHR (2005) require re-vaccination at ten-year intervals if indicated, in order to retain a valid ICVP.

### Contraindications

(Specific contraindications should be reviewed in the SPC)

- Age five months and younger
- Persons with a history of a severe allergic reaction to any component of the vaccine including anaphylaxis to egg protein
- Immunocompromised hosts
- Thymus disorder, including myasthenia gravis, thymoma, thymectomy, and DiGeorge syndrome [23]

### Precautions

(Expert advice should be sought prior to immunising individuals in these groups)

- Infants age six to eight months
- Febrile illness
- HIV-infected individuals
- Pregnant women
- Breast feeding women
- Individuals age 60 years and older

### Adverse events

The 17D strain virus YF vaccine has been in use for more than 50 years. It is estimated that 300-400 million doses of the vaccine have been administered worldwide [24]. Reactions to YF vaccine are usually mild and short lived. They include myalgia, headache, and low-grade fever, typically occurring during the first five to ten days post vaccination, and will affect 10-30% of recipients.



Serious adverse events are rare and fall into three main categories: hypersensitivity reactions, vaccine-associated neurologic disease (YEL-AND) and vaccine-associated viscerotropic disease (YEL-AVD).

### **Hypersensitivity reactions**

The vaccine is propagated in chick embryos. Vaccine stabilizers may include beef gelatin 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 doses administered [25].

### **Yellow Fever Vaccine-Associated Neurologic Disease (YEL-AND)**

Post-vaccine encephalitis has been recognised as a rare event since the early use of the vaccine. It was particularly seen in infants; early reports documented an incidence of 0.5 to 4 cases per 1,000 infants under the age of six months [26]. Since 2001, a new pattern of neurologic adverse events was recognized [27-29]. These events have been termed YF vaccine-associated neurologic disease (YEL-AND). The clinical presentation of neurologic events begins four to 23 days (median 14 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 who had no underlying YF immunity.

## Yellow Fever Vaccine-Associated Viscerotropic Disease (YEL-AVD)

YF vaccine-associated viscerotropic (YEL-AVD) disease is a syndrome of fever and multi-organ failure that resembles severe YF disease; it was first described in 2001 [30-32]. Two to eight days (median four days) following vaccination, patients develop fever, malaise, headache, and myalgias that progress to hepatitis, hypotension, and multi-organ failure. Death has occurred in more than 60% of reported cases. As with neurologic disease, all cases have occurred in primary vaccinees. Thymus disorders and thymectomy are documented risk factors and all patients with thymus disorders should not receive vaccine.

Based on reported cases and the number of doses of YEL distributed, the US has estimated the risk of neurologic disease to be about five cases per million doses and viscerotropic disease to be four cases per million doses [33]. These estimates are similar to those made based on cases reported in Europe [28].

For individuals who are aged 60 years and older, the current risk for neurologic and viscerotropic adverse events increases by several fold, such that these severe adverse events occur at a rate of about 25 cases per million doses [34].

There is no evidence that YEL-AVD is related to reversion of the vaccine virus to a more virulent form [35].

These two patterns of serious adverse events appear to be host related. The highest rates of YEL-AND occur in the very young and those aged over 60 years of age [26,29]. Host factors for YEL-AVD are not well understood, but it is clear that those with existing thymus disease and those of increasing age are at more risk [28,34]. Other possible host factors, such as genetic susceptibility have been postulated and are being investigated [35,36].

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