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Yellow fever

NOTIFIABLE

The disease

Yellow fever is an acute flavivirus infection spread by the bite of an infected mosquito. The disease occurs in tropical Africa and South America (see maps on the website of the National Travel Health Network and Centre (NaTHNaC), www.nathnac.org); it has never been reported in Asia despite the presence of the vector. Two epidemiological patterns of yellow fever are recognised – urban and jungle – although the disease is clinically and aetiologically identical. In urban yellow fever, the viral reservoir is man and the disease is spread between humans by the *Aedes aegypti* mosquitoes that live and breed in close association with humans. Jungle yellow fever is transmitted among non-human hosts (mainly monkeys) by forest mosquitoes. Humans may become infected when they enter into the forest habitat and can become the source of urban outbreaks. Yellow fever can reappear with outbreaks after long intervals of apparent quiescence. Rural populations are at greatest risk of yellow fever but in recent years urban outbreaks have occurred both in West Africa and South America.

Yellow fever ranges in severity from non-specific, self-limited symptoms of fever, malaise, photophobia and headache to an illness of sudden onset with fever, vomiting and prostration which may progress to jaundice and haemorrhage. In local populations in endemic areas, the overall fatality ratio is about 5%, rising to 20 to 30% once jaundice and severe symptoms occur. In non-immune travellers and migrants, and during epidemics in areas that have low levels of yellow fever activity, the case fatality rate can exceed 50% (Monath, 2004). The incubation period is generally three to six days but may be longer. Death usually occurs seven to ten days after the onset of illness.

There is no specific treatment for yellow fever. Preventive measures such as the eradication of *Aedes* mosquitoes, protection from mosquito bites, and immunisation reduce the risk. Jungle yellow fever can only be prevented by immunisation and personal protection against mosquito bites because of the wide range and distribution of mosquito vectors and mammalian hosts.

There is no risk of transmission in the UK from imported cases since the mosquito vector does not occur in the UK.

History and epidemiology of the disease

Sequence analysis of the viral genome suggests that yellow fever virus originated in Africa about 3000 years ago (Zanotto *et al*., 1996). However, the earliest record of an epidemic was in the Yucatan in Mexico in 1648. The term 'yellow fever' was first used in an outbreak that occurred in Barbados in 1750. The disease became a major problem in the colonial settlements of the Americas and West Africa in the 1700s and was repeatedly introduced into sea ports of the United States and Europe during this time (Monath, 2004).

Transmission of yellow fever by mosquitoes was first postulated by Josiah Clark Nott in 1848 and confirmed by Walter Reed and colleagues in Cuba in 1900. The live, attenuated vaccine that remains in use today was developed in the 1930s. Control of the urban vector, combined with a highly effective vaccine, had reduced human cases, particularly in South America, but there has been a resurgence of the disease in the last decade with at least 200,000 cases estimated to occur annually (Robertson *et al*., 1996; Monath, 2001).

The yellow fever vaccination

Yellow fever vaccine is a live, attenuated preparation of the 17D strain of yellow fever virus grown in specific pathogen-free embryonated chick eggs. Each 0.5ml dose contains not less than 1000 mouse LD_{50} units.

Storage

Vaccines should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

Presentation

The yellow fever vaccine is available as a lyophilised powder for reconstitution with a diluent.

Yellow fever vaccines are thiomersal-free. They contain live organisms which have been attenuated (modified).

Dosage and schedule

First dose is 0.5ml. Further doses should be given at the recommended intervals if required.

Administration

The vaccines should be reconstituted with the diluent supplied by the manufacturer and either used within an hour or discarded.

Doses of 0.5ml of yellow fever vaccine should be given by deep subcutaneous injection irrespective of age.

Yellow fever vaccine can be given at the same time as other inactivated and live vaccines. The vaccines should be given at separate sites, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine was given should be noted in the patient's records.

If yellow fever vaccine cannot be given at the same time as another live vaccine, it should be given at an interval of four weeks.

Disposal

Equipment used for vaccination, including used vials or ampoules, should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box (UN-approved, BS 7320).

Recommendations for the use of the vaccine (including re-immunisation)

The objectives of the immunisation programme are to provide a minimum of one dose of yellow fever vaccine for individuals at risk of yellow fever and to prevent the international spread of yellow fever. The latter aims to prevent infected individuals introducing the virus into areas where the presence of mosquito vectors and an appropriate host could support the establishment of yellow fever.

A single dose correctly administered confers immunity in 95 to 100% of recipients. Immunity persists for at least ten years and possibly for life (Groot and Riberiro, 1962; Rosenzweig *et al*., 1963; Poland *et al*., 1981).

The following groups should be immunised:

- laboratory workers handling infected material
- persons aged nine months or older who are travelling to countries that require an International Certificate of Vaccination for entry
- persons aged nine months or older who are travelling to or living in infected areas or countries in the yellow fever endemic zone (see maps on www.nathnac.org), even if these countries do not require evidence of immunisation on entry.

Immunisation should be performed at least ten days prior to travel to an endemic area to allow protective immunity to develop and for the International Certificate of Vaccination (if required) to become valid.

Reinforcing immunisation

Re-immunisation every ten years is recommended for those at risk, although the vaccine is considered to confer longer protection.

Risk assessment for travel

With the recent recognition of rare severe adverse events related to yellow fever vaccine (Centers for Disease Control and Prevention (CDC), 2002; Kitchener, 2004), it is critical to make a careful risk assessment prior to administering vaccine. In general, the risk from yellow fever for travel to a yellow fever endemic region outweighs the risk associated with the vaccine (World Health Organization (WHO), 2004). Itineraries should be scrutinised to ensure that the vaccine is given only to those considered at risk from the disease. In general, the risk of yellow fever from travel to endemic regions of Africa is ten times higher than the risk from travel to South America (Monath, 2004, Monath and Cetron, 2002), but risk depends entirely on itinerary, season of travel and planned activities.

Although the risk is small, infants under nine months are at higher risk of vaccine-associated encephalitis, with the risk being inversely proportional to age. Infants aged six to nine months should only be immunised if the risk of yellow fever during travel is unavoidable; expert opinion should be sought in these situations. Infants aged five months or younger should never be immunised (Monath, 2004). Advice on the avoidance of mosquito bites should be given (see contraindications).

Further details about the recommendations for travellers are contained in *Health information for overseas travel* (Department of Health, 2001) and may be found on the NaTHNaC, www.nathnac.org.

Yellow fever certificate

Under the International Health Regulations (both those of 1969, and those of 2005, which are due to come into force in June 2007), states may require immunisation against yellow fever. A valid International Certificate of Vaccination is required as evidence. Country requirements are published annually by WHO in *International travel and health* (available at www.who.int/ith) (WHO, 2004), and are included in *Health information for overseas travel* (Department of Health, 2001).

The International Certificate of Vaccination is valid for ten years beginning from the tenth day after primary immunisation and immediately after re-immunisation if re-immunisation occurs within the ten-year period.

Contraindications

There are very few individuals who cannot receive yellow fever vaccine when it is recommended. When there is doubt, appropriate advice should be sought from a travel health specialist.

The vaccine should not be given to:

- those aged five months or under
- those who have had a confirmed anaphylactic reaction to a previous dose of yellow fever vaccine
- those who have had a confirmed anaphylactic reaction to any of the components of the vaccine
- those who have had a confirmed anaphylactic reaction to egg
- those who have a thymus disorder

and also to:

- patients considered immunocompromised due to a congenital condition, disease process or treatment (see Chapter 6).

Patients with any of the conditions described above who must travel should be informed of the risk of yellow fever and instructed in mosquito avoidance measures. For those who intend to visit countries where an International Certificate of Vaccination against yellow fever is required for entry, a letter of exemption should be issued by the Yellow Fever Vaccination Centre or by the practitioner treating the patient. This should be taken into consideration by the port health authorities at the destination.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation.

If an individual is acutely unwell, immunisation should be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any sign or symptoms to the adverse effects of the vaccine.

People over 60 years of age

The risk for neurologic and viscerotropic adverse events increases with age (see below). The risk assessment needs to take account of this.

Pregnancy

Yellow fever vaccine should not be given to pregnant women because of the theoretical risk of fetal infection from the live virus vaccine. Pregnant women should be advised not to travel to a high-risk area. When travel is unavoidable, the risk from the disease and the theoretical risk from the vaccine have to be assessed on an individual basis. WHO states that vaccination against yellow fever may be considered in early pregnancy depending upon the risk (WHO, 2012). Two studies in which pregnant women have been vaccinated demonstrated no adverse fetal outcomes (Nasidi *et al*., 1993; Tsai *et al*., 1993), but transplacental transmission has occurred in early pregnancy (Tsai *et al*., 1993). A slightly increased risk of spontaneous abortion in women vaccinated in early pregnancy has been suggested (Nishioka *et al*., 1998). Antibody titres following vaccination are lower in pregnant women (Nasidi *et al*., 1993). Women who continue to be at risk once the pregnancy is completed should be revaccinated.

Inadvertent vaccination during early pregnancy is not an indication for termination (Monath, 2004).

Breast-feeding

There is some evidence of transmission of live vaccine virus to infants under two months of age from breast milk. As noted earlier, infants aged five months and under should not be immunised and infants aged six to nine months should only be immunised if the risk of yellow fever during travel is unavoidable; expert opinion should be sought in these situations. Therefore, expert advice should be sought from NaTHNaC (www.NaTHNaC.org) or Health Protection

Scotland (www.Travax.nhs.uk) before administering yellow fever vaccine to women who are breastfeeding.

Immunosuppression and HIV infection

Unless the yellow fever risk is unavoidable, asymptomatic HIV-infected persons should not be immunised. There is limited evidence from data, however, that yellow fever vaccine may be given safely to HIV-infected persons with a CD4 count that is greater than 200 and a viral load that is suppressed (Receveur *et al*., 2000; Tattevin *et al*., 2004). Specialist advice should be sought in these cases. The antibody response in HIV positive persons may be diminished (Sibailly *et al*., 1997). (See Chapter 6.)

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk), the British HIV Association (BHIVA) *Immunisation guidelines for HIV-infected adults* (BHIVA , 2006) and the Children's HIV Association of UK and Ireland (CHIVA) Immunisation guidelines (www.bhiva.org/chiva).

Adverse reactions

Adverse reactions following yellow fever vaccine are typically mild and consist of headache, myalgia, low grade fever and/or soreness at the injection site and will occur in 10 to 30% of recipients (Monath, 2004; Freestone *et al*., 1977; Lang *et al*., 1999; Monath *et al*., 2002). Injection site reactions tend to occur from days one to five after immunisation. Systemic side effects also occur early but may last up to two weeks (Monath *et al*., 2002). Up to 1% of individuals may need to alter daily activities. Reactions are more likely to occur in persons who have no prior immunity to yellow fever virus (Monath *et al*., 2002; Moss-Blundell *et al*., 1981).

Rash, urticaria, bronchospasm and anaphylaxis occur rarely. In a passive surveillance system in the US, the rate of anaphylaxis following yellow fever vaccine was estimated to be one case per 130,000 doses of vaccine (Kelso *et al*., 1999). Reactions are most likely related to egg protein in the vaccine. It is possible that some persons are sensitive to and react to the gelatin that is used as a stabiliser in this vaccine as well as in other vaccines.

Post-vaccine encephalitis has been recognised as a rare event since the early use of the vaccine. It was particularly seen in infants (see above), and early reports indicated an incidence of 0.5 to 4 cases per 1000 infants under six months of age (Monath, 2004). Since 2001, a new pattern of neurological adverse events was recognised that occurred in older individuals (CDC, 2002; Kitchener, 2004).

When this was recognised, a retrospective review revealed other cases that occurred in the 1990s. These events have now been termed yellow fever vaccine-associated neurological disease (YEL-AND). The clinical presentation of this new pattern of neurological events begins four to 23 days following receipt of vaccine with the onset of fever and headache that may progress to include one or more of confusion, focal neurological deficits, coma and Guillain-Barré syndrome. CSF in these cases demonstrates a pleocytosis with increased protein and when, tested, yellow fever virus-specific IgM antibody. The clinical course is usually for complete recovery. All cases have occurred in primary vaccinees who have no underlying yellow fever immunity.

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is a newly recognised syndrome of fever and multi-organ failure that resembles severe yellow fever, first described in 2001 (CDC, 2001; Chan *et al*., 2001; Martin *et al*., 2001a; Vasconcelos *et al*., 2001). Two to seven 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. Vaccine-derived virus has been isolated from several of the cases and yellow fever viral antigen has been detected in post-mortem samples (Martin *et al*., 2001a). As with YEL-AND, all cases have occurred in primary vaccinees without underlying yellow fever immunity. In the reports of viscerotropic disease, 17% have had a history of thymus disease with subsequent thymectomy (Barwick Eidex, 2004). Thus, all patients with thymus disorders should not receive vaccine (see Contraindications on p 447).

Based on reported cases and the number of doses of yellow fever vaccine distributed, the US has estimated the risk of neurological disease to be about four cases per million doses and viscerotropic disease to be three cases per million doses (Cetron *et al*., 2002). These estimates are similar to those made based on cases reported in Europe (Kitchener, 2004). Based on the current evidence, for individuals who are aged 60 years or older, the risk of neurological and viscerotropic adverse events increases several-fold, such that neurological events occur at a rate of about 17 cases per million doses and viscerotropic events at a rate of 20.5 cases per million doses (Martin *et al*., 2001b; Marfin *et al*., 2005).

All suspected reactions in children and severe suspected reactions in adults should be reported to the Commission on Human Medicines through the Yellow Card scheme.

Yellow fever vaccination centres

Yellow fever vaccine may be administered only at 'designated' centres as established by the International Health Regulations of WHO.

In England and Wales, the Department of Health and Welsh Assembly Government have devolved responsibility for administering yellow fever vaccination centres (YFVCs) to NaTHNaC, an organisation established in 2003 that is dedicated to providing information to health professionals and setting standards in travel medicine.

A listing of approved YFVCs in England and Wales may be found at: www.nathnac.org/yellowfevercentres.aspx?comingfrom=professional.

Information on becoming a YFVC, including attendance at a yellow fever vaccine training seminar and clinical information about travel medicine, can be obtained on the NaTHNaC website, www.nathnac.org.

Practitioners in Scotland should apply to:

Health Protection Scotland Travel Health Section (Yellow Fever)
Clifton House, Clifton Place
Glasgow G3 7LN
www.hps.scot.nhs.uk
Administrative enquiries:
Telephone - 0141 300 1948
Email: nss.hps.yellowfever@nhs.net

Practitioners in Northern Ireland should apply to:

Linda Hutcheson
Health Protection Team
Department of Health
Social Services and Public Safety
Room C4.22
Castle Buildings
Stormont
Belfast BT4 3PP
(Tel: 028 9052 2118
E-mail: Linda.Hutcheson@dhsspsni.gov.uk)

Supplies

All vaccines used to protect against yellow fever must be approved by WHO. One WHO-approved licensed vaccine is currently available in the UK – Stamaril™ (Sanofi Pasteur MSD, Tel: 0800 085 5511).

The vaccine is supplied to designated centres only for injection as freeze-dried powder and solvent.

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