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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 parts of the tropical and sub-tropical regions of Africa and South and Central America (including Trinidad) (see maps on the website of the National Travel Health Network and Centre (NaTHNaC), https://travelhealthpro.org.uk/); it has never been reported in Asia despite the presence of the vector. Three epidemiological patterns of yellow fever are recognised – urban, savannah 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 primarily by the *Aedes aegypti* mosquitoes that live and breed in close association with humans. In Africa, an intermediate (savannah) cycle exists that involves transmission of virus from mosquitoes to humans living or working in jungle border areas. In this cycle, the virus can be transmitted from monkey to human or from human to human via mosquitoes. 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 urban outbreaks do occur in Africa. Urban populations in South and Central America are also at risk due to city centres being re-infested with *A.aegypti* and increased population movement in to and out of endemic areas.

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. Infection results in lifelong immunity in those who recover.

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 yellow fever 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). A more recent study of disease burden in Africa estimated there to be 130,000 (95% CI 51,000-380,000) cases of severe YF in 2013, resulting in 78,000 (95% CI 19,000-180,000) deaths (Garske *et al*.,2014).

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 LD50 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 of reconstituted vaccine. 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 or intramuscular injection irrespective of age.

Yellow fever vaccine can be given at any time in relationship to other inactivated and live vaccines (Public Health England, 2015). However, in the case of co-administration with MMR vaccine there are some data to suggest sub optimal antibody responses against yellow fever, mumps and rubella antigens (Nascimento *et al*., 2011). Where possible these two vaccines should be given 28 days apart. 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.

Disposal

Equipment used for vaccination, including used vials, ampoules or syringes, should be disposed of by placing it in a proper, puncture-resistant 'sharps' box according to local authority regulations and guidance in Health Technical Memorandum 07-01: Safe management of healthcare waste (Department of Health, 2013).

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. Data suggests that with some exceptions, most vaccine recipients will maintain protective antibody titers for potentially several decades, or possibly life-long, following vaccination (WHO Strategic Advisory Group of Experts (SAGE), 2013).

The following groups should be immunised:

- laboratory workers handling infected material
- persons aged nine months or older who are travelling to or living in countries that require an International Certificate of Vaccination or Prophylaxis (ICVP) for entry
- persons aged nine months or older who are travelling to or living in areas or countries with a risk of yellow fever transmission (see YF vaccination maps on https://travelhealthpro.org.uk/), 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 ICVP (if required) to become valid. However, vaccine should still considered for last minute travellers who should be counselled about the importance of insect bite precautions and possible implications of an invalid ICVP.

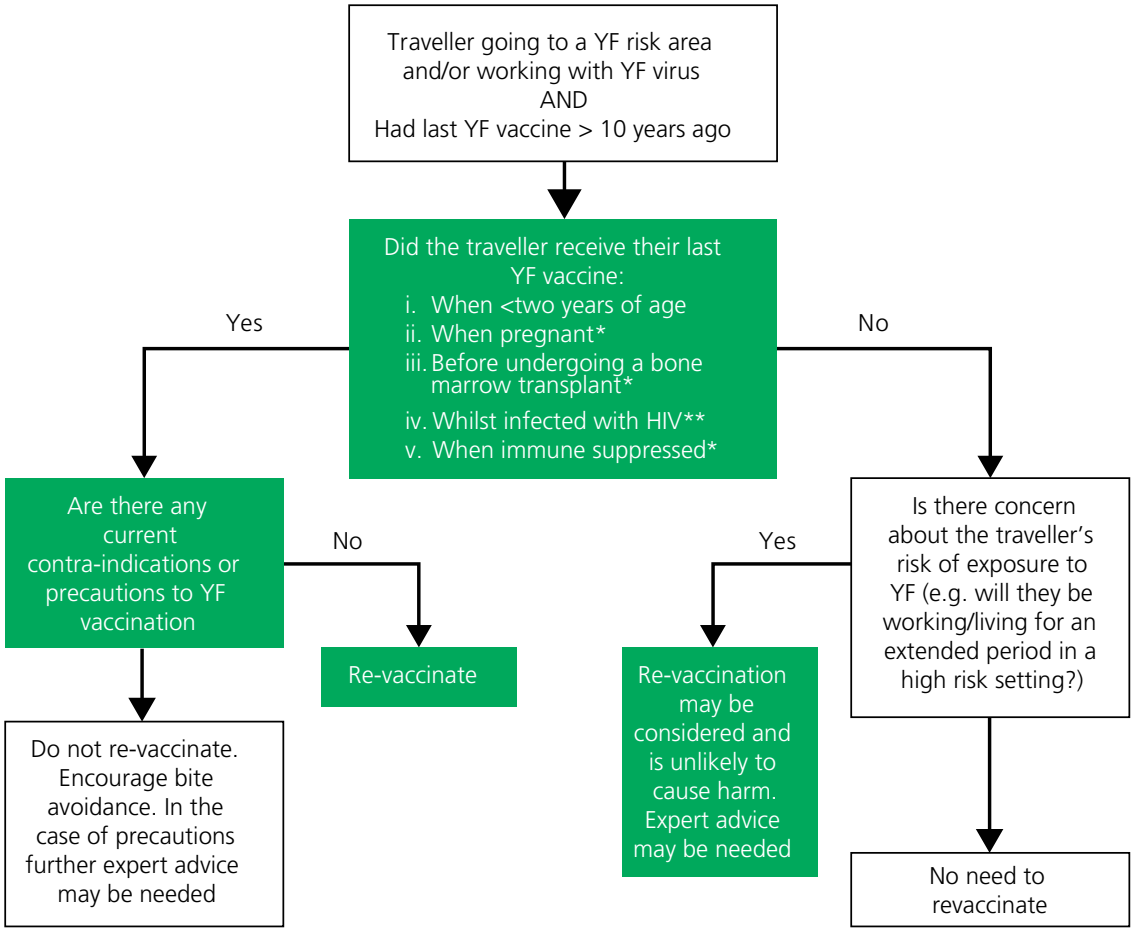
Reinforcing immunisation

The WHO Strategic Advisory Group of Experts (SAGE) on Immunization state that (based on currently available data, a single dose of yellow fever vaccine appears to confer life-long protective immunity against yellow fever disease. Therefore, with some exceptions, a booster dose of yellow fever vaccine is not needed to maintain immunity WHO Strategic Advisory Group of Experts (SAGE), 2013).

Reinforcing immunisation should be offered to a small subset of individuals at continued risk who may not have developed long term protection from their initial yellow fever vaccination (see Figure 35.1). This includes those who received their initial yellow fever vaccination:

- when aged less than two years old
- during pregnancy
- whilst infected with HIV
- when immune suppressed
- before undergoing a bone marrow transplant

Figure 35.1 Reinforcing immunisation



*Note time of revaccination should be based on individual assessment of ongoing risk, and may be considered before 10 years assuming there are no contraindications

**Please also refer to BHIVA guidance

In certain situations where there is concern about a traveller's risk of exposure to yellow fever (e.g. working/living for an extended period in a high risk setting) a booster dose of YF vaccine can be considered – expert advice can be sought from NaTHNaC (https://travelhealthpro.org.uk/) or Health Protection Scotland (www.Travax.nhs.uk)

From 11 July 2016 (for all countries), the yellow fever vaccine certificate (ICVP) will be valid for the duration of the life of the person vaccinated. WHO state that a valid certificate, presented by arriving travellers, cannot be rejected on the grounds that more than ten years have passed since the date vaccination became effective as stated on the certificate; and that boosters or revaccination cannot be required (WHO, 2016).

Risk assessment for travel

With the 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. Itineraries should be scrutinised to ensure that the vaccine is given only to those considered at risk from the disease and to those who require an ICVP (see below). 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 (WHO, 2013), 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 less than six months should never be immunised (Monath *et al.*, 2013). Advice on the avoidance of mosquito bites should be given (see contraindications below).

Further details about the recommendations for travellers may be found on the NaTHNaC website, https://travelhealthpro.org.uk/.

International Certificate of Vaccination or Prophylaxis

Under the International Health Regulations 2005, member states may require immunisation against yellow fever as a condition of entry. A valid ICVP is required as evidence. Country requirements are published annually by WHO in *International travel and health* (available at www.who.int/ith) , and on the NaTHNaC country information pages http://travelhealthpro.org.uk/countries.

As of 11 July 2016, The ICVP is valid for the lifetime of the person vaccinated beginning from the tenth day after primary immunisation.

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 under six months
- 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, including egg.
- those who have a history of thymus disorder or thymectomy*
- patients with primary or acquired immunodeficiency due to a congenital condition, disease process or treatment (see below)

* To date there is no evidence of increased risk of yellow fever vaccine–associated serious adverse events in people who have undergone incidental surgical removal of their thymus (e.g. during cardiac surgery) or have had indirect radiation therapy in the distant past. People who had incidental removal of their thymus after the age of one year may therefore receive a yellow fever vaccine following a detailed risk assessment. A cautious approach is recommended for those who had incidental removal of their thymus before the age of one year. In these cases further advice should be sought.

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 ICVP 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.

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.

Precautions

People over 60 years of age

The risk for neurologic and viscerotropic adverse events increases with age (see below). Vaccination can be given to those aged 60 years and older following careful risk assessment.

Pregnancy

Yellow fever vaccine should not generally 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. 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). WHO state that in areas where yellow fever is endemic, or during outbreaks, the benefits of vaccination are likely to far outweigh the risk of vaccine. Pregnant women should be counselled on the potential benefits and risks

of vaccination so that they may make an informed decision (WHO, 2013). Women who continue to be at risk once the pregnancy is completed should be revaccinated.

Breast-feeding

There is some evidence of transmission of live vaccine virus to infants under two months of age from breast milk. For women who are breast-feeding children under the age of nine months expert advice should be sought from NaTHNaC (https://travelhealthpro.org.uk/) or Health Protection Scotland (www.Travax.nhs.uk) before administering yellow fever vaccine.

Infants

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 less than six months should never be immunised (Monath *et al*., 2013). Advice on the avoidance of mosquito bites should be given (see contraindications above).
Infants aged six to nine months should only be immunised following a detailed risk assessment. For this age group, vaccination is generally only recommended when risk of yellow fever transmission is considered to be high such as during epidemics/outbreaks. If travel is unavoidable; expert opinion should be sought on whether to vaccinate.

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 reinforcing immunisation Figure 35.1 and **Chapter 6**).

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk), the British HIV Association guidelines for immunization of HIV-infected adults 2015 (BHIVA, 2015: http://bhiva.org/vaccination-guidelines.aspx) and the Children's HIV Association of UK and Ireland (CHIVA) Immunisation guidelines (http://www.chiva.org.uk/guidelines/immunisation/).

Many adults with chronic inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, psoriasis, glomerulonephritis) will be on stable long term low dose corticosteroid therapy (defined as up to 20mg prednisolone per day for more than 14 days in an adult or 1mg/kg/day in children under 20kg) either alone or in combination with other immunosuppressive drugs. Long term stable low dose corticosteroid therapy, either alone or in combination with low dose non-biological oral immune modulating drugs (e.g. methotrexate 25mg per week in adults or up to 15mg/m2 in children, azathioprine 3.0mg/kg/day or 6-mercaptopurine 1.5mg/kg/day), are not considered sufficiently immunosuppressive and these patients can generally receive live vaccines. However in the case of yellow fever vaccine data is limited, and a cautious approach is recommended. Specialist advice may be sought in these circumstances.

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 (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 reporting rate of anaphylaxis following yellow fever vaccine was estimated to be 13 per 100,000 doses distributed (Lindsey *et al*., 2016). 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 some yellow fever vaccines 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, *et al*., 2013). 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 two to 56 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. Almost all cases have occurred in primary vaccinees who have no underlying yellow fever immunity.

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is a 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). One to 18 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, four out of 23 cases (17%) had had a history of thymus disease with subsequent thymectomy (Barwick Eidex, 2004). Thus, all patients with thymus disorders or those who have had a thymectomy should not receive vaccine (see Contraindications section above).

Based on reported cases and the number of doses of yellow fever vaccine distributed, the reporting rate in the US is 0.8 and 0.3 per 100,000 doses for neurological disease and viscerotropic disease respectively (Lindsey *et al.*, 2016). 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, and are reported at a rate of about 2.2 and 1.2 per 100,000 doses respectively (Lindsey *et al.*, 2016).

All suspected reactions in children and severe suspected reactions in adults should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card scheme.

Yellow fever vaccination centres

Yellow fever vaccine can only be administered at 'designated' yellow fever vaccination centres (YFCVs) as established by the International Health Regulations of WHO.

In England,Wales, and Northern Ireland, the Department of Health, the Welsh Assembly Government, and Department of Health, Social Services and Public Safety, Northern Ireland have devolved responsibility for administering YFVCs to National Travel Health Network and Centre (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, Wales, and Northern Ireland (EWNI) can be found at: http://nathnacyfzone.org.uk/search-centres

Information on becoming a YFVC in EWNI, including mandatory yellow fever vaccine training clinical information about travel medicine, can be obtained on the NaTHNaC website, at https://travelhealthpro.org.uk/

Practitioners in Scotland should apply to:

Health Protection Scotland Travel Health Section (Yellow Fever) NHS National Services Scotland
4th Floor Meridian Court 5 Cadogan Street
Glasgow G2 6AT

www.hps.scot.uk

Administrative enquiries: Telephone - 0141 300 1948 Email: nss.hps.yellowfever@nhs.net

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, Tel 01483 505515, http://www.sanofi.co.uk)

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

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