Yellow fever vaccination

Gerard Flaherty

What GPs need to know when advising international travellers to yellow fever-endemic countries

ONE OF THE TOPICS which generated the most interest at this year’s ICGP Summer School workshop devoted to travel medicine was that of yellow fever vaccination. I frequently receive queries from travel medicine practitioners about yellow fever distribution and vaccine safety. This article will hopefully shed some light on this important, and often confusing subject.

Epidemiology

Yellow fever (YF) is a viral haemorrhagic fever caused by a flavivirus related to Japanese encephalitis virus and transmitted by the bite of an infected Aedes or Haemagogus mosquito, which acquires the virus by feeding on infected non-human or human primates. Infected humans are themselves infectious to mosquitoes if the latter take a blood meal shortly before the onset of fever and for three to five days afterwards.

Clinical infection varies from a mild, non-specific febrile illness to severe disease with jaundice and haemorrhage. The disease occurs throughout sub-Saharan Africa and tropical South America, where it is endemic, with intermittent epidemics. The majority of outbreaks in Africa have occurred in West Africa but an increased number of cases have been reported in recent years from Central African countries. Most cases in South America are reported from the Orinoco, Amazon and Araguaia river basins, with the highest cumulative incidence occurring in Bolivia and Peru. No cases of YF have been reported from North America and Europe since the early 1900s and, while transmission has never been identified in Asia or Australia, these regions are at risk for importation of the virus, as many of their urban areas have both the vector Aedes aegypti, as well as large non-immune human populations. This explains why certain non-endemic countries such as India and Australia require proof of YF vaccination from travellers arriving from YF-endemic countries.

The World Health Organization estimates that 200,000 cases of YF occur annually, with case-fatality ratios of approximately 20% in Africa and 50% in South America, the latter due to enhanced diagnostic testing rather than increased disease virulence. Management is supportive, with patients requiring critical care support with mechanical ventilation or haemodialysis if there is multisystem organ involvement.

Risk to international travellers

Between 1970 and 2009, there were nine reported cases of YF in unvaccinated travellers from Europe and the US who had travelled to West Africa (five cases) or South America (four cases); eight of these nine travellers died. The risk for a traveller of contracting the virus depends on immunisation status, mosquito bite avoidance, location of travel, duration of exposure, recreational activities, and the local rate of virus transmission, which shows an increased risk in the mid-to-late rainy season in West Africa and South America. Crude estimates of the risks of illness and death due to YF for the unvaccinated traveller are 10 deaths out of 50 cases per 100,000 population for West Africa, and one death out of five cases per 100,000 population for South America.

Yellow fever vaccine

For international travel, YF vaccine must be administered at a designated and registered YF vaccination centre which is regulated in the Republic of Ireland by the HSE under authority from the Minister of Health. YF vaccine was first developed in the 1930s and two live attenuated sub-strain vaccines, administered by subcutaneous injection, are in current use. Once reconstituted, a multi-dose vial of YF vaccine must be maintained at 2°-8°C and either administered or discarded within one hour. No human efficacy studies have been performed with YF vaccines, but their protective benefit is supported by multiple scientific observations. Studies show that 80-100% of vaccinated people develop protective neutralising antibodies by day 10 following vaccination. This explains why International Health Regulations mandate that proof of YF vaccination as a condition of entry for travellers arriving from certain countries becomes valid only after 10 days have elapsed between administration of the vaccine and arrival at the border of the host country.

The YF vaccination certificate is valid for 10 years, although this recommendation may be revised in the future based on recent evidence demonstrating long-term persistence of YF antibodies. YF vaccine is generally well tolerated, with the most common systemic side effects in one large study being mild headache (33% of subjects), myalgia (25%), malaise (19%) and fever (15%). Rates of anaphylaxis to a component of YF vaccine vary in studies from 0.8 to 1.8 events per 100,000 doses administered. Yellow fever-vaccine associated neurologic disease and yellow fever vaccine-associated viscerotropic disease are serious but rare adverse effects of YF vaccine, occurring in 0.8 and 0.4 cases per 100,000 doses administered, respectively. The rate of both syndromes is higher in vaccinees aged over 60 years, making advanced age a precaution to the use of the vaccine. Following receipt of YF vaccine, patients should be advised not to donate blood for at least two weeks. There is no evidence...
that co-administration of inactivated vaccines interferes with the immune response to YF vaccine but other live viral vaccines should be given either simultaneously or one month apart.

**Certificate of vaccination or prophylaxis**

Where a medical contraindication exists to the administration of YF vaccine (see Table 1), a licensed physician may issue a medical waiver by completing and signing the Medical Contraindications to Vaccination section of the International Certificate of Vaccination or Prophylaxis, which was last updated in December 2007. In addition, the traveller should be advised to obtain specific advice from the embassy of the destination country or countries, as acceptance of the medical waiver is not guaranteed by the destination country. The vaccination certificate itself must be complete and accurate in every detail as a legal document in order to be valid. Failure to secure validation can lead to quarantine for up to six days, revaccination, or denial of entry of the traveller. The certificate becomes valid 10 days after the date of primary vaccination, or immediately following revaccination if documentation exists showing that the previous vaccine was given with the last 10 years. Travellers should be advised to carry this certificate with their passport when crossing relevant international borders. I frequently go a step further and advise travellers attending my clinic to carry both passport and certificate in a sealed Ziploc® bag, especially during the rainy season!

Certain countries require vaccination from travellers arriving from all countries, even non-endemic European countries (see Table 2), while other countries require evidence of vaccination only from travellers who have last visited a country with risk of YF transmission. Recommendations are subject to change at any time because of changes in YF virus circulation and the prescriber is advised to consult an authoritative source such as CDC (www.cdc.gov/travel) or TRAVAX (http://www.travax.nhs.uk/) for updated information.

The global maps for YF transmission were revised in 2010 and four categories of risk for YF virus transmission were described: endemic, transitional, low potential for exposure, and no risk. YF vaccine is recommended for travel to endemic and transitional areas and for a subset of travellers to areas with low potential for exposure, such as those with prolonged travel, significant likely mosquito exposure, or inability to avoid mosquito bites.

The revised YF maps (Figures 1 and 2) depict areas where YF vaccination is currently recommended. Proof of YF vaccination should not be required if travelling from a country with a low potential for exposure (for example, Tanzania) to a country with a vaccination entry requirement (for example, Kenya), with an important exception being South Africa where, since 2011, YF vaccination has been required for travellers arriving from, or transiting for over 12 hours through any of the five countries with low potential for exposure (Eritrea, São Tomé and Príncipe, Somalia, Tanzania, and Zambia), as well as

---

**Table 1: Contraindications and precautions to the administration of yellow fever vaccine**

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allergy to a vaccine component (eg, egg)</td>
<td>• Age 6-8 months</td>
</tr>
<tr>
<td>• Age &lt;6 months</td>
<td>• Age ≥60 years</td>
</tr>
<tr>
<td>• Symptomatic HIV infection or CD4 count &lt;200/mm³</td>
<td>• Asymptomatic HIV infection and CD4 count 200-499/mm³</td>
</tr>
<tr>
<td>• Thymus disorder associated with abnormal immune function</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Primary immunodeficiencies</td>
<td>• Breastfeeding</td>
</tr>
<tr>
<td>• Malignancy</td>
<td>-</td>
</tr>
<tr>
<td>• Organ transplantation</td>
<td>-</td>
</tr>
<tr>
<td>• Immunosuppressive and immunomodulatory drugs (eg, methotrexate, or prednisolone ≥20mg daily for &gt;2 weeks)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2: Countries requiring proof of yellow fever vaccination from all arriving travellers**

*(as of August 7, 2013)*

- Angola
- Benin
- Burkina Faso
- Burundi
- Cameroon
- Central African Republic
- Congo, Republic of
- Côte d’Ivoire
- Democratic Republic of the Congo
- French Guiana
- Gabon
- Ghana
- Guinea-Bissau
- Liberia
- Mali
- Niger
- Rwanda
- São Tomé and Príncipe
- Sierra Leone
- Togo
those with risk of YF virus transmission. This is an important consideration for your travellers who visit the Victoria Falls on the border between Zambia and Zimbabwe before returning to Johannesburg, for example, in South Africa, to connect to their return flight to Europe.

**Conclusion**

Travel medicine physicians should vaccinate only travellers who are at risk for exposure to YF virus (ie. consider the itinerary and the distribution of YF within endemic countries) or who require documentation of vaccination for entry; they should observe the contraindications and precautions to use of the YF vaccine; and should communicate clear information to the traveller about the risk of the disease and the safety profile of the vaccine.

Gerard Flaherty is the current President of the Travel Medicine Society of Ireland and is senior lecturer in Clinical Medicine at NUI, Galway

**References**


