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CHAPTER 8

Yellow fever

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Epidemiology

Yellow fever (YF) virus is transmitted to humans primarily through the bite of an infected *Aedes* or *Haemagogus* sp. mosquito. The virus is present in sub-Saharan Africa and tropical South America, where it is endemic and intermittently epidemic [1]. The World Health Organization (WHO) estimates that 200,000 cases of YF, including 30,000 deaths, occur annually worldwide.

YF virus has three transmission cycles: sylvatic (jungle), intermediate (savannah), and urban [2]. Most YF disease in humans is due to sylvatic or intermediate transmission cycles. However, urban YF occurs periodically in Africa and sporadically in the Americas.

In Africa, most outbreaks have been reported from West Africa, with fewer outbreaks being reported from Central and East Africa [2]. YF virus transmission in rural West Africa is seasonal, with an elevated risk during the end of the rainy season and the beginning of the dry season (usually July–October) [3]. However, YF virus may be episodically transmitted by *Ae. aegypti* even during the dry season in both rural and densely settled urban areas [2].

In South America, transmission of YF virus occurs predominantly in sparsely-populated forested areas. Consequently, YF occurs most frequently in unimmunized young men who are exposed to mosquitoes through work in forested areas [2]. The risk for infection in South America is highest during the rainy season (January–May) [3].

Clinical manifestation, diagnosis, and treatment

Most people infected with YF virus are asymptomatic. For symptomatic illness, the incubation period is typically 3–6 days. The initial illness presents as a non-specific febrile illness with sudden onset of fever, headache, myalgias, nausea, and vomiting [2]. Most patients improve after the initial presentation; however, approximately 15% of patients progress, after a brief remission of hours to 1 day, to more severe

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disease with jaundice, hemorrhagic symptoms, and multisystem organ failure. The case–fatality ratio for patients with hepatorenal dysfunction is 20–50% [2].

The preliminary diagnosis is based on the patient’s clinical features and travel details. Laboratory diagnosis is typically made by detecting virus-specific immunoglobulin M (IgM) antibodies, followed by confirmation by more specific antibody testing, such as a plaque reduction neutralization test. Samples collected in the first few days of the illness may be positive by YF virus isolation or nucleic acid amplification tests.

No specific medications are available to treat YF virus infections; treatment is supportive (e.g., rest, fluids, analgesics, and antipyretics).

Yellow fever among travelers

A traveler’s risk for acquiring YF is determined by various factors, including immunization status, travel details, and local rate of virus transmission at the destination during the time of travel [4]. Although reported cases of human disease are the principal indicator of disease risk, case reports may be absent because of a low level of transmission, a high level of immunity in the population (e.g., because of vaccination), or insensitive surveillance. This “epidemiologic silence” does not equate to absence of risk and should not lead to travel without protective measures.

From 1970 through 2012, nine YF cases were reported in unvaccinated travelers from the United States and Europe and one in a vaccinated traveler [2]. Eight of the nine unvaccinated travelers died and the vaccinated traveler survived.

For a 2-week stay, the estimated risks for illness and death attributable to YF for an unvaccinated traveler visiting an endemic area of West Africa are 50 and 10 cases per 100,000, respectively; for South America, the risks for illness and death are 5 and 1 case per 100,000, respectively [3].

Prevention

All travelers to YF-endemic countries should be advised of the disease risk and prevention methods, including personal protective measures and vaccine.

Personal protection measures

All travelers should take precautions to avoid mosquito bites, including using insect repellent, wearing permethrin-impregnated clothing, and staying in accommodations with screened or air-conditioned rooms [5].

Vaccines

All YF vaccines currently manufactured are live-attenuated viral vaccines. YF vaccine is recommended for people aged 9 months or more who are traveling to or living in areas with risk for YF virus transmission in South America and Africa [6,7]. In

addition, some countries require proof of YF vaccination for entry. To minimize the risk of serious adverse events, clinicians should observe the contraindications to and precautions for vaccination and vaccinate only persons who are at risk for exposure or are visiting a country that requires proof of vaccination for entry [6].

Vaccine administration

For persons of all ages for whom vaccination is indicated, a single subcutaneous injection of reconstituted vaccine should be administered. In 2013, the World Health Organization (WHO) stated that a single dose of YF vaccine is sufficient to confer life-long protective immunity against YF disease, and a booster dose is not necessary [6]. However, the International Health Regulations (IHR) continue to require revaccination at 10-year intervals. Therefore, clinicians and travelers should review country entry requirements, including for booster doses, prior to traveling [7].

Vaccine safety and adverse reactions

Reactions to YF vaccine are generally mild; 10–30% of vaccinees report mild systemic adverse events, including low-grade fever, headache, and myalgias [2].

Three well-characterized serious adverse events occur following YF vaccine administration: immediate hypersensitivity or anaphylactic reactions, YF vaccine-associated neurologic disease (YEL-AND), and YF vaccine-associated viscerotropic disease (YEL-AVD) [4].

- Immediate hypersensitivity reactions are characterized by rash, urticaria, and/or bronchospasm. Anaphylaxis after YF vaccine is reported to occur at a rate of 0.8–1.8 cases per 100,000 doses distributed.
- YEL-AND manifests as distinct clinical syndromes, including meningoencephalitis, Guillain-Barré syndrome, and acute disseminated encephalomyelitis. Illness onset is 3–28 days after vaccination, and almost all cases have been reported in first-time vaccinees [4]. YEL-AND is rarely fatal. The incidence of YEL-AND among US travelers is reported to be 0.4–0.8 per 100,000 doses distributed [4].
- YEL-AVD is similar to wild-type disease, with widespread vaccine virus dissemination, and often multisystem organ failure and death [4]. More than 60 cases have been reported worldwide. Symptom onset is 0–8 days after vaccination, and all cases have been reported in first-time vaccinees. The case-fatality ratio is 63% [2]. The incidence of YEL-AVD among US travelers is 0.3–0.4 cases per 100,000 doses of vaccine distributed [4].

Contraindications

Persons who have a contraindication to YF vaccination should be not vaccinated and should avoid travel to YF-endemic areas. If travel to endemic areas is unavoidable, the clinician should provide a medical waiver and inform the traveler of increased risk for YF associated with lack of vaccination, and also protective measures.

Infants younger than 6 months

YF vaccine is contraindicated for infants aged <6 months because of a relatively high rate of YEL-AND documented in vaccinated young infants [2].

Hypersensitivity

YF vaccine is contraindicated for people with a history of hypersensitivity to any of the vaccine components, including eggs, egg products, chicken proteins, and gelatin. Skin testing and desensitization can be performed (see the vaccine package insert) in persons needing vaccination but for whom there is a concern about hypersensitivity reaction to the vaccine.

Altered immune status

YF vaccine is contraindicated for people with altered immune status caused by any of the following conditions [4,6]:

- Thymus disorder associated with abnormal immune cell function, such as thymoma or myasthenia gravis.
- AIDS or other clinical manifestations of HIV, including people with CD4T-lymphocyte values $<200/\text{mm}^3$ or $<15\%$ of total lymphocytes for children aged <6 years.
- Primary immunodeficiencies, malignant neoplasms, and transplantation.
- People whose immunologic response is either suppressed or modulated by current or recent radiation therapies or drugs. Drugs with known immunosuppressive or immunomodulatory properties include, but are not limited to, high-dose systemic corticosteroids, alkylating drugs, antimetabolites, tumor necrosis factor- α inhibitors, interleukin blocking agents, and other monoclonal antibodies targeting immune cells [5]. If these therapies are discontinued, YF vaccine should be deferred until immune function has improved.

Family members of people with altered immune status, who themselves have no contraindications, can receive YF vaccine.

Precautions

If a person who has a condition that is considered a precaution to YF vaccination cannot postpone or avoid travel to YF-endemic countries, vaccination can be considered based on weighing risk versus benefits. If international travel requirements, not risk of YF, are the only reason for vaccination, the person should be excused from YF immunization and issued a waiver.

Infants aged 6–8 months

Age 6–8 months is a precaution for YF vaccination. Two cases of YEL-AND have been reported among infants aged 6–8 months [4].

Adults 60 years of age or older

Age 60 years or more is a precaution for YF vaccination because the reporting rate for YEL-AND and YEL-AVD is increased among people aged 60 years or more [4]. Given that YEL-AND and YEL-AVD are seen almost exclusively in primary vaccinees, caution should be exercised with older travelers who are receiving their first YF vaccination.

Asymptomatic HIV infection with moderate immune suppression

Asymptomatic HIV infection with CD4T-lymphocyte values $200\text{--}499/\text{mm}^3$ or $15\text{--}24\%$ of total lymphocytes for children aged <6 years is associated with moderate

immune suppression and hence is a precaution for YF vaccination. The relatively few observational studies performed have reported no serious adverse events following YF vaccination among patients considered moderately immunosuppressed based on their CD4 counts.

Note. If an asymptomatic HIV-infected person has no evidence of immune suppression based on CD4 counts (CD4 T-lymphocyte values $\geq 500/\text{mm}^3$ or $\geq 25\%$ of total lymphocytes for children aged <6 years), YF vaccine can be administered if recommended.

Pregnancy

Pregnancy is a precaution for YF vaccine administration. The safety of YF vaccination during pregnancy has not been studied in a large prospective trial. However, among pregnant women who received YF vaccination, limited studies have found no major malformations in their infants, and results are conflicting regarding an association with spontaneous abortions. The seroconversion rate among women vaccinated during pregnancy is variable and might depend on the trimester of vaccination. Although there are no specific data, women should be advised to wait 4 weeks after YF vaccination before conceiving.

Breastfeeding

Breastfeeding is a precaution for YF vaccine administration. Three YEL-AND cases have been reported in exclusively breastfed infants, aged <1 month, whose mothers were vaccinated with YF vaccine [2].

Simultaneous administration of other vaccines

Because no evidence exists that inactivated vaccines interfere with the immune response to YF vaccine, they can be administered either simultaneously or at any time before or after YF vaccination. YF vaccine should be given simultaneously or 30 days apart from other live-virus vaccines because the immune response to one live-virus vaccine might be impaired if administered within 30 days of another live-virus vaccine [6]. However, oral typhoid vaccine can be administered simultaneously or at any interval before or after YF vaccine.

International certificate of vaccination or prophylaxis (ICVP)

The IHR allow countries to require proof of YF vaccination from travelers, even if only in transit, arriving from a country with risk of YF virus transmission, to prevent importation and indigenous spread of YF virus [7]. Some countries require evidence of vaccination from all entering travelers [5]. Travelers without proof of YF vaccination who arrive in a country with a YF vaccination entry requirement may be quarantined for up to 6 days, refused entry, or vaccinated on-site.

As proof of YF vaccination, all vaccinees should possess a completed International Certificate of Vaccination or Prophylaxis (ICVP) validated with the provider's signature and the YF vaccination stamp of the administering YF vaccination center [5].

The ICVP must be signed by a medical provider supervising the administration of the vaccine, who may be a licensed physician or a healthcare worker designated by the physician.

An incomplete ICVP is not considered valid, and the traveler could be treated the same as a person without proof of vaccination at the port of entry. The ICVP is valid for 10 years, beginning 10 days after the date of vaccination. When a booster dose of the vaccine is given within this 10-year period, the certificate is considered valid from the date of revaccination.

Medical waivers (exemptions)

A traveler who has a specific contraindication to YF vaccine and who cannot avoid travel to a country requiring vaccination should be issued a waiver before departure. The clinician issuing a waiver should fill out and sign the Medical Contraindications to Vaccination section of the ICVP and give the traveler a signed and dated exemption letter on letterhead stationery. The letter should clearly state the contraindications to vaccination and bear the stamp of the YF vaccination center. The clinician should also inform the traveler of the increased risk for YF associated with lack of vaccination and how to minimize this risk by avoiding mosquito bites. Reasons other than medical contraindications or precautions are not acceptable for exemption from vaccination. The traveler should be advised that issuance of a waiver does not guarantee its acceptance by the destination country.

Requirements versus recommendations

Country entry requirements for proof of YF vaccination under the IHR differ from YF vaccination recommendations, such as those published by the WHO [5,7]. YF vaccine entry requirements are established by countries to prevent the importation and transmission of YF virus. Travelers must comply with these to enter the country, unless they have been issued a medical waiver. Country requirements are subject to change at any time; therefore, travelers are encouraged to check with the relevant embassy or consulate before departure.

YF vaccine recommendations are advice given by public health authorities to prevent YF virus infections among travelers. Recommendations are subject to change at any time because of changes in YF virus circulation, and travelers should check relevant websites for updates.

YF risk classification for travelers

The four categories of risk for YF virus transmission apply to all geographic areas: endemic, transitional, low potential for exposure, and no risk [1]. YF vaccination is recommended for travel to endemic and transitional areas. Although vaccination is generally not recommended for travel to areas with low potential for exposure, it

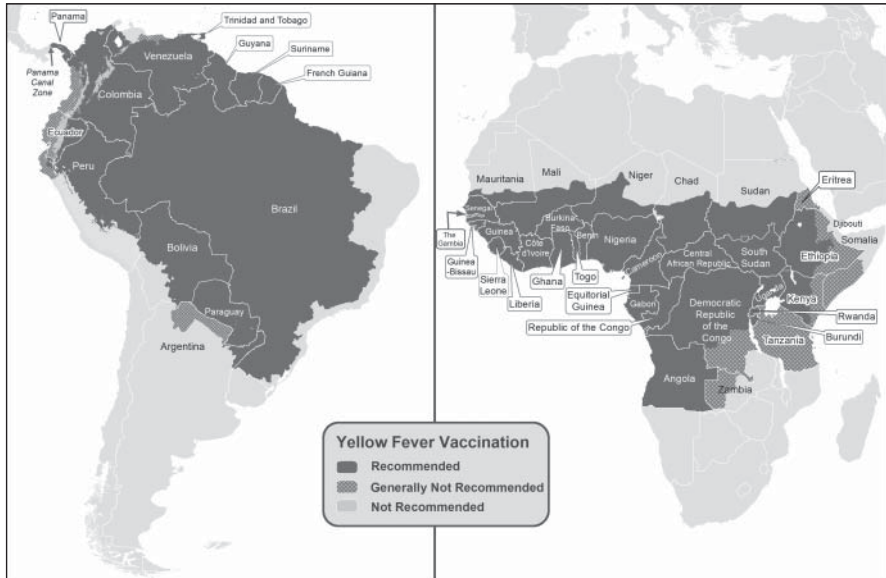


Figure 8.1 Yellow fever vaccine recommendations. Source: Adapted from Centers for Disease Control and Prevention 2014 [5].

might be considered for a small subset of travelers who may be at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites.

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