Yellow Fever: Epidemiology and Prevention

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Yellow fever continues to occur in regions of Africa and South America, despite the availability of effective vaccines. Recently, some cases of severe neurologic disease and multiorgan system disease have been described in individuals who received yellow fever vaccine. These events have focused attention on the need to define criteria for judicious use of yellow fever vaccine and to describe the spectrum of adverse events that may be associated with yellow fever vaccine. Describing host factors that would increase risk of these events and identifying potential treatment modalities for yellow fever and yellow fever vaccine–associated adverse events are subjects of intense investigation.

Yellow fever is a viral hemorrhagic fever with high mortality that is transmitted by mosquitoes. The disease occurs now only in Africa and Central and South America, although historically, large outbreaks occurred in Europe and North America. Mosquitoes capable of transmitting yellow fever exist in regions where the disease does not presently occur and in regions, such as Asia, where yellow fever has never occurred. Vector-control strategies that were once successful for elimination of yellow fever from many regions have faltered, leading to reemergence of the disease. Consequently, immunization is now the most important method of prevention of yellow fever, supplemented with prevention of mosquito bites.

Effective vaccines against yellow fever have been available for almost 70 years and are responsible for a significant reduction of occurrences of the disease worldwide. Currently, available vaccines protect against all yellow fever virus strains and are attenuated live virus vaccines derived from a virus originally isolated in 1927. This virus strain was attenuated by passage in mouse embryo tissue culture and then in chicken embryo tissue culture, resulting in the 17D strain from which all current vaccines are derived. Recently, newly recognized, serious—but rare—adverse events associated with yellow fever vaccine have been described and have prompted investigation of the mechanisms of these adverse reactions and clarification of the most appropriate indications for yellow fever vaccine.

EPIDEMIOLOGY

Approximately 200,000 cases of yellow fever occur annually; 90% of them occur in Africa. A dramatic resurgence of yellow fever has occurred since the 1980s in both sub-Saharan Africa and South America [1]. A series of epidemics and smaller outbreaks of yellow fever that occurred in West African countries were primarily responsible for the increased incidence of yellow fever in Africa, but the first epidemic reported in Kenya in >2 decades signaled that a change in the distribution of the disease was also occurring. Transmission in Africa is maintained by a high density of vector mosquito populations that are in close proximity to largely unvaccinated human populations. Although some countries have incorporated yellow fever vaccine into childhood immunization programs, vaccine coverage is not optimal.

In South America, the rate of transmission of yellow fever is lower than in Africa, in part because high vaccine coverage occurs primarily as part of mass immunization campaigns in response to outbreaks of the disease. The largest outbreak of yellow fever in South America since the 1950s occurred in Peru in 1995, and cases were reported in Bolivia, Brazil, Colombia, Ecuador, and Peru from 1985 to 1994. Resurgence of the disease in Brazil during the late 1990s and early 2000s prompted mass vaccination campaigns. Factors that were related to the resurgence of yellow fever in South America included relatively low vaccine coverage in areas where outbreaks of the disease occurred, migration of susceptible individuals to forested regions where the disease is transmitted, and increasing urbanization.
of the disease [2, 3]. Accurate data about burden of yellow fever are difficult to obtain because of underreporting of the disease (especially from isolated areas), limitations of passive surveillance, lack of diagnostic capability in many regions where yellow fever is endemic, and occurrence of asymptomatic infection. Such challenges bolster support for immunization programs as the mainstay of prevention.

Yellow fever has occurred in unvaccinated travelers. During 1970–2002, 9 cases were reported in unimmunized travelers from the United States and Europe; disease was acquired in Brazil (3 cases), Senegal (2 cases), Venezuela, Ivory Coast, the Gambia, and West Africa. Mortality rate was 89%. Another case occurred during 1987 in an immunized traveler from Spain who visited 4 West African countries [4, 5]. Estimation of risk of yellow fever associated with travel is made difficult by fluctuation of disease by year and season, vaccine coverage of the local population (which makes it more challenging to estimate risk for the unimmunized), and incomplete surveillance data. Regions with current risk for yellow fever are shown in figures 1 and 2.

**CLINICAL DESCRIPTION OF YELLOW FEVER**

The presentation of yellow fever disease ranges from subclinical infection to systemic disease including fever, jaundice, hemorrhage, and renal failure. Differences in virus strains, as well as incompletely understood host immune factors, are likely responsible for the range of clinical symptoms. Viremia peaks 2–3 days after infection, and patients with fatal cases have a longer duration of viremia than do survivors.
Three phases of yellow fever are described. The first, during which virus is present in blood, is characterized by fever, malaise, generalized myalgia, nausea, vomiting, irritability, dizziness, and a generally toxic appearance. Laboratory abnormalities include leukopenia, present at the onset of illness, and elevation of serum transaminase levels on days 2–3 of illness—before the onset of jaundice. The second phase is characterized by improvement in symptoms, including a reduction of fever; this may last up to 48 h but is not noted in all cases. Some infected individuals recover at this phase without developing jaundice. The third phase occurs in ~15% of cases and is characterized by the return of fever, nausea, vomiting, jaundice, and bleeding diathesis. Antibodies appear in the blood as virus disappears. Multiorgan system involvement is typical. Serum transaminase levels are proportional to the severity of disease; they peak early during the second week of illness in patients who recover. Case-fatality rates vary widely but were in the range of 20% for West African patients with jaundice in several studies [6].

Infancy and older age are associated with increased severity and lethality of infection with yellow fever virus. Genetic factors play a role in susceptibility and immune response to flaviviruses in mice; such factors are poorly understood in humans and are the subject of current investigation [6]. Findings that a single
nucleotide polymorphism in genes for 2′–5′-oligoadenylate synthetase was associated with susceptibility to severe disease with another flavivirus (West Nile virus) and that deficiency of CCR5 (a monocyte and T lymphocyte chemokine receptor) increased risk of symptomatic West Nile virus infection suggest that genetic factors may also be important with regard to susceptibility to yellow fever virus [7, 8].

**YELLOW FEVER VACCINES**

**Vaccine Development**

Efforts to develop yellow fever vaccines began soon after the isolation of the virus in 1927. Efforts to produce inactivated vaccines during the early 20th century were unsuccessful, and subsequent vaccine development focused on live virus products. Use of the French neurotropic vaccine began in the 1930s and proved to be effective—especially for curtailling epidemic disease in West African countries—but this vaccine was discontinued in 1982 because of the unacceptably high incidence of adverse events, especially encephalitis.

All current yellow fever vaccines derive from the 17D strain. During the initial phase of yellow fever vaccine production in the United States and Brazil during 1937–1941, 2 main lineages of the 17D line (17D–204 and 17DD) were used for vaccine production [6]. Recognition that continued serial passage could result in substrains with unacceptably high rates of adverse events led to the adoption of the “seed lot” system of vaccine production. Primary and secondary seed lots were prepared and characterized, and all vaccine lots were prepared from a single passage from the secondary seed. In 1957, the World Health Organization published *Requirements for Yellow Fever Vaccine*, which standardized the seed lot and manufacturing procedures. New seed lots are tested for neurovirulence and viscerotropism before being used for vaccine production. The vaccine contains no antibiotics or preservatives (such as thimerosal), but some preparations do contain gelatin [6].

**Vaccine Response**

Vaccination against yellow fever produces high levels of protection, with seroconversion rates of >95% in children and adults and duration of immunity of ≥10 years [9]. Ninety percent of vaccine recipients develop neutralizing antibody within 10 days after immunization, and 99% develop neutralizing antibody within 30 days. Although immunity is likely to be lifelong after a single dose, international health regulations recommend revaccination at 10-year intervals for those who remain at risk.

Serologic response to yellow fever vaccine is not diminished by simultaneous administration of tetanus, diphtheria, pertussis, measles, polio, bacille Calmette-Guérin, hepatitis A, hepatitis B, Vi antigen capsular polysaccharide typhoid, oral Ty21a typhoid, or oral cholera vaccines [5]. Data on response to yellow fever vaccine when administered with Japanese encephalitis vaccine are lacking, although prior infection with Japanese encephalitis does not interfere with protection from yellow fever. Prior dengue infection may decrease response to yellow fever vaccine [5]. Immune globulin did not decrease the antibody response to yellow fever vaccine when given 0–7 days before immunization [10]. Chloroquine does not adversely affect the antibody response to yellow fever vaccine [11].

Mild viremia occurs 3–7 days after immunization in individuals receiving their first dose of yellow fever vaccine and lasts for 1–3 days. Elevations in levels of IFN-α, TNF-α, and markers of T cell activation occur at this time and are likely mediators of common mild adverse effects of yellow fever vaccine. Resolution of viremia occurs as neutralizing antibody develops. Viremia does not occur with subsequent doses of vaccine, and adverse effects are milder. No data are available about level or duration of viremia in children or immunosuppressed individuals [6].

**Common Adverse Effects**

Adverse effects associated with yellow fever vaccine are generally mild and include headaches, myalgia, and low-grade fever, which occurred 5–10 days after immunization in <25% of persons who participated in clinical trials [12, 13].

**Severe Adverse Events**

Cases of severe multiorgan failure after receipt of yellow fever vaccine were reported beginning in 1996 and raised awareness of the medical community to adverse events associated with yellow fever vaccine. Identifying the spectrum of adverse events and risk factors for severe reactions is the subject of intense investigation. The 3 kinds of severe adverse events associated with yellow fever vaccine are immediate hypersensitivity reactions, neurotropic disease, and viscerotropic disease.

Hyper-sensitivity reactions. Yellow fever vaccine is prepared in embryonated eggs, and persons with an egg allergy should not receive vaccine. Individuals who are able to eat eggs or egg products can receive vaccine. Systemic allergic reactions, such as anaphylaxis and urticaria, have been reported in 1 in 58,000–131,000 individuals after administration of yellow fever vaccine [14]. Sensitivity to other vaccine components—especially gelatin—may play a role in these events.

Yellow fever vaccine–associated neurotropic disease (YEL-AND). YEL-AND (formerly known as “postvaccinal encephalitis”) was, in the past, the most common severe adverse event associated with yellow fever vaccine, especially in infants. From 1945 (when the seed lot system for vaccine development was introduced) to 2002, encephalitis was reported in 23 patients worldwide among >200 million doses of distributed vaccine. Sixteen cases occurred in newborns and infants <9 months of age [15]. The incidence of YEL-AND in very young infants is...
incidence is 1 case per 40,000–50,000 doses [17]. An update
immunized for the first time at the age of
YEL-A VD is 1 case per 200,000–300,000 doses; for persons
immunization, although cases have also occurred in younger
million distributed doses.
fever in Brazil in 1975 suggests that this syndrome has been
suspected cases of viscerotropic disease and 4 cases of neuro-
encephalitis and Guillain Barré syndrome, in addition to encephalitis [19].

Yellow fever vaccine–associated viscerotropic disease (YEL-
During 1996–2001, a syndrome that manifested with
fever, jaundice, and multiple organ system failure after receipt of
yellow fever vaccine was reported in 10 patients worldwide
5 to 79 years [18, 20–25]. This syndrome—initially called
severe multisystem failure and death and may include neurotropic disease. Symptoms begin 2–5 days after
immunization, and the syndrome is notable for fever, elevated
hepatocellular enzyme levels, respiratory failure, blood dyscra-
asias, and in some cases, renal failure. In 2002, 2 additional
suspected cases of viscerotropic disease and 4 cases of neuro-
tropic disease were reported among US recipients of yellow
fever vaccine [26]. As of 2004, the total number of cases world-
wide was 26; additional cases continue to be reported, including
a fatal case reported in 2005 that involved a 22-year-old woman
[27]. Although YEL-AVD was first identified in 1996, charac-
terization of a yellow fever virus strain as vaccine-derived in a
case of what was thought initially to be a fatal case of yellow
fever in Brazil in 1975 suggests that this syndrome has been
present for at least several decades [28]. Initial crude estimates
incidence of YEL-AVD in the range of 3–5 cases per
million distributed doses.

A study of reports submitted to the Vaccine Adverse Event
Reporting System in the United States identified advanced age
as a risk factor for adverse events associated with yellow fever
immunization, although cases have also occurred in younger
individuals [29]. The Centers for Disease Control and Preven-
tion Vaccine Information Statement states that the incidence of
YEL-AVD is 1 case per 200,000–300,000 doses; for persons
immunized for the first time at the age of ≥60 years, the
incidence is 1 case per 40,000–50,000 doses [17]. An update
of advanced age as a risk factor for serious adverse events
associated with yellow fever vaccine was published in 2005
and affirms the increased risk and documents a reporting rate ratio
of 5.9 (95% CI, 1.6–22.2) in persons aged ≥60 years receiving
yellow fever vaccine for the first time, compared with those
aged 19–29 years [30].

Disease of the thymus gland has been identified as a possible
risk factor for developing severe reactions after yellow fever
vaccine. Fifteen percent of 26 individuals with YEL-AVD had
a history of thymus disease, including thymoma and myasthe-
nia gravis [31].

YEL-AVD is characterized by a widespread inflammatory re-
sponse with exuberant viral replication. Antibody levels are
significantly higher than expected. Examination of tissue spec-
imens obtained from patients who had fatal cases of YEL-AVD
reveals widespread dissemination of yellow fever vaccine virus
and active viral replication in multiple organs [6, 27]. Sequenc-
izing studies do not identify mutations in vaccine virus to explain
these adverse events [6]. The occurrence of 2 cases in 1 family
in Brazil supports the hypothesis that host genetic factors may
be associated with predisposition to yellow fever vaccine–
associated adverse events [6].

Treatment of YEL-AND and YEL-AVD. There are no stan-
dardized treatment protocols for treatment of adverse events
associated with yellow fever vaccine. Supportive care remains
the mainstay of treatment, and patients should be managed in
settings where intensive care is available.

Information about potential treatment modalities is available
from studies of treatment of yellow fever in humans and from
animal models and retrospective epidemiologic studies of yel-
low fever vaccine–associated adverse events. Rhesus monkeys
were protected from yellow fever virus challenge when given
yellow fever antiserum; administration of immune serum after
onset of clinical disease had no beneficial effect [6]. Clinical
experience with use of immune globulin in cases of YEL-AVD
has not been promising, but use of the product very early
during the clinical illness, when there remains potential for
affecting the level of viremia, has not been studied. Use of
interferons for prevention and treatment of yellow fever is lim-
ited by the need to use these products before infection or during
the incubation period to have therapeutic benefit [6]. Ribavirin
therapy is active in vitro against yellow fever, but high doses
are required to achieve a beneficial effect. Ribavirin therapy was
ineffective in monkey and mouse models but showed reduced
mortality in a hamster model [32]. A retrospective study of
corticosteroid therapy among 11 case patients infected with
YEL-AVD identified a higher rate of survival among patients
receiving stress-dose steroid regimens (3 [75%] of 4 patients),
compared with those who received no steroids or high- or low-
dose steroid regimens (2 [29%] of 7 patients) [33].
Indications, Precautions, and Contraindications for Yellow Fever Immunization

Travelers to countries or regions where there is increased risk of infection with yellow fever should receive a single dose of vaccine at least 10 days before departure, unless there are specific contraindications (table 1) [4, 15, 16, 34]. Yellow fever vaccine must be given at official yellow fever vaccine centers and documented with an International Certificate of Vaccination (valid from 10 days through 10 years after the date of immunization). Vaccine is contraindicated absolutely in newborns and infants aged <6 months, should be given to infants aged 6–9 months only if the risk of disease is significant and other methods of prevention cannot be employed, and should be used cautiously in infants aged 9–12 months. The single most important step for judicious use of yellow fever vaccine is to immunize only individuals traveling to regions where yellow fever is endemic (1 report describes multiorgan system failure in 2 individuals who received yellow fever vaccine and traveled to regions where yellow fever had never been reported [20]). Individuals should also use personal protective measures to prevent mosquito bites.

History of thymus disease is a contraindication to yellow fever vaccine [16]. Immunocompromised individuals also should not be immunized. Asymptomatic HIV-infected individuals who have a CD4 cell count ≥200 cells/mm$^3$ and who face increased risk of yellow fever infection and cannot avoid potential exposure should be offered the choice of immunization [16, 35]. Individuals immunized for the first time at the age of ≥60 years appear to be at increased risk for adverse events associated with yellow fever vaccine. Individuals who have a family member who sustained a severe adverse event to yellow fever vaccine may also be at increased risk for adverse events. Use of yellow fever vaccine in such individuals requires careful review of risk during the travel itinerary and elucidation of information about the nature of the adverse event in the family member.

The safety of yellow fever immunization during pregnancy has not been established, and little is known about the potential of vaccine-associated virus strains to infect the fetus [36]. Fetal infection was documented in 1 of 41 infants exposed to maternal vaccination, and an increased risk of spontaneous abortion was found in a Brazilian study of 39 pregnant women who were immunized with yellow fever vaccine, compared with 74 control patients who did not receive yellow fever vaccine [37, 38]. Immunization during pregnancy may result in antibody concentrations inferior to those obtained after immunization of nonpregnant women [39]. A mass vaccination campaign in Brazil during early 2000 resulted in the inadvertent immunization with 17DD vaccine of 480 pregnant women who were observed until the infants were 1 year of age. Maternal seroconversion was high, and no infants were found to be infected at birth (no IgM antibodies were detected, and no placental or umbilical cord blood specimens were found to contain yellow fever vaccine virus strain by PCR) [40]. Therefore, yellow fever immunization should be avoided during pregnancy, except when there is a clear and unavoidable increased risk of infection.

There are no reports of transmission of yellow fever vaccine virus from nursing mothers to their infants, and it is not known whether yellow fever vaccine virus is excreted into breast milk. Lactating women who travel to regions where yellow fever is endemic and whose risk of yellow fever infection exceeds the theoretical risk of transmission of vaccine virus to their infants may be immunized [16].

**CONCLUSIONS**

Yellow fever continues to occur in regions of Africa and South America. Recent descriptions of serious adverse events that are associated with yellow fever vaccine have lent new urgency to defining criteria for judicious use of yellow fever vaccine. Future research is focused on defining the spectrum of adverse events that are associated with yellow fever vaccine and the host factors that would increase risk of these events and on identifying potential treatment modalities for yellow fever and for yellow fever vaccine–associated viscerotropic and neurotropic diseases.

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**Table 1. Yellow fever vaccine contraindications and precautions.**

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<tr>
<th>Contraindications</th>
<th>Precautions</th>
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<tbody>
<tr>
<td>Age, &lt;6 months</td>
<td>Age, 6–12 months</td>
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<td>Thymus disease or history of thymus disease</td>
<td>Age, ≥60 years for first-time vaccinees</td>
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<td>Lactation</td>
<td>Lactation</td>
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<td>Asymptomatic HIV infection with laboratory verification of adequate immune system function</td>
<td>Hypersensitivity to eggs</td>
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<td>Hypersensitivity to gelatin</td>
<td>Hypersensitivity to gelatin</td>
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<tr>
<td>Family history of adverse events associated with yellow fever vaccine</td>
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References